ADHERENCE TO AN ONCOLOGY CLINICAL PRACTICE GUIDELINE

by

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Abstract

Background and Purpose: In 2014, a multidisciplinary breast cancer group developed and disseminated a clinical practice guideline to assist surgeons in choosing eligible patients, with locally advanced or inflammatory breast cancer, for whom a referral should be sent to medical oncology for consideration of neoadjuvant treatment. However, it was unclear whether surgeons had been adhering to this guideline. The purpose of this practicum was to compare the neoadjuvant referral rates pre- and post-guideline dissemination and evaluate the effects of patient/tumor/facility-related factors on surgeons' decision to refer.

Methods: (1) literature review; (2) consultation with key stakeholders; (3) chart review; and (4) recommendations.

Results: The factors of interest and methods were informed by the literature review and the consultations. During the chart review process, data were collected on 47 and 54 patient cases from 2013 (pre-guideline) and from 2016 (post-guideline), respectively. All patient cases of inflammatory breast cancer were referred for both study years. In contrast, the referral rates for all cases of locally advanced breast cancer was 23.3% and 26.9%. In 2016, patients were more likely to be referred if they had positive lymph node involvement, AJCC stages of IIIA and IIIC, triple negative subtypes, or received definitive surgery at university-affiliated hospitals.

Conclusion: There has been little to no improvement for guideline adherence between the study years and the referral rates for eligible patients were poor. Future efforts to clarify the guideline and improve referral appear to be warranted.

Keywords: Guideline adherence, neoadjuvant therapy, breast cancer

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Introduction

The Eastern Health Breast Disease Site Group (BDSG) has been developing and disseminating clinical practice guidelines for the screening, diagnosis and management of breast cancer within Eastern Health and for the provincial Cancer Care Program of Newfoundland and Labrador for several years. However, limited resources had prevented any meaningful measurement of outcomes from the development of these clinical practice guidelines. At a recent monthly BDSG meeting, the concern was raised that some eligible patients with newly diagnosed, locally advanced breast cancer were not being referred by surgeons to the discipline of medical oncology for a discussion regarding neoadjuvant therapy. This is contradictory to the recommendations of a BDSG guideline entitled "*Neoadjuvant Treatment of Primary Breast Cancer"* approved on July 4, 2014 by the Cancer Care Program and which had been disseminated to all surgeons in the province of Newfoundland and Labrador (NL). The group suggested that this practicum project would be an excellent opportunity to determine whether this guideline was having any impact on the number of patient referrals from surgeons for consideration of neoadjuvant therapy within the province of Newfoundland and Labrador.

Background

The 2010 American Joint Committee on Cancer (AJCC) staging manual, 7th ed., describes the staging of cancer as being based on the TNM system, where T denotes the size of the tumor, N as the extent of lymph node invasion, and M as the presence (or absence) of metastatic spread of disease (Edge et al., 2010). According to the Eastern Health BDSG guideline, locally advanced breast cancers are defined as having disease with either a "…primary tumor greater than 5 cm in diameter or that involves the skin or

chest wall" (represents a T3 or T4 tumor size), or "… (those) with fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement" (representing a N2 or greater), or both without evidence of distant metastatic spread (Eastern Health, 2014, p.10). According to Singletary et al. (2002), the AJCC staging system also recognizes locally advanced breast cancer to be any stage III (e.g., T3N1M0, T1N2M0) or one subset of stage IIB (i.e., T3N0M only). A copy of the 7th edition of the AJCC breast cancer staging guide, located in Appendix A, outlines the T sizes, nodal (N) and metastases (M) classifications. Inflammatory breast cancer, a T4 disease, is also a subtype of locally advanced breast cancer however due to its distinct biology and clinical presentation, it is typically always considered separately. The Eastern Health neoadjuvant guideline describes inflammatory breast cancer as a rare and particularly aggressive type of disease characterized by erythema and edema of the breast which gives the breast a peau d'orange or orange peel appearance (2014).

Neoadjuvant therapy is antineoplastic therapy (e.g., chemotherapy, hormonal therapy, monoclonal antibodies, or occasionally, radiation therapy) which is administered prior to definitive surgery (e.g., lumpectomy, partial mastectomy, total mastectomy), in an effort to reduce tumor burden and produce an improved surgical result. Adjuvant therapy, on the other hand, is the use of antineoplastic therapy after the definitive surgery has taken place. Neoadjuvant therapy has been used for many years to treat patients with inflammatory breast cancer or those who are not surgical candidates due to extensive local disease.

Early research has indicated that there has been no survival advantage (disease-free survival or overall survival) for the use of neoadjuvant therapy over that of adjuvant

therapy however, neoadjuvant therapy has been found to offer other advantages which adjuvant treatment cannot (Mauri, Pavlidis, & Ioannidis, 2005; Mieog, van der Hage, & van de Velde, 2007). Neoadjuvant therapy has the potential to shrink tumor size; improve the cosmetic surgical result; allow for in vitro assessment of tumor response to treatment; provide individualized treatment at a systemic level earlier; and downstage the axilla to allow sentinel node biopsy in select cases (Buzdar et al, 2005; Gianni et al, 2010; Teshome & Hunt, 2014; Zhang & Hurvitz, 2016).

There have been many developments in the diagnosis and treatment of breast cancer in last forty years with the discovery of predictive tumor biomarkers and molecular subtyping, and the introduction of targeted therapy agents. Recent evidence from two meta-analyses has suggested that neoadjuvant therapy can offer some survival advantage for patients diagnosed with breast cancers having a human epidermal growth receptor (HER2) positive or triple negative subtype (Broglio et al., 2016; Houssami, Macaskill, von Minckwitz, Marinovich, & Mamounas, 2012). Specialized pathology testing can detect the presence/absence of hormonal and tyrosine kinase receptors on the surface of breast cancer cells which allow the identification of HER2 positive and triple negative breast cancers. HER2 positive subtypes would be breast cancers that are negative for estrogen (ER) and progesterone receptors (PR) but over-express the HER2 receptor, while a triple negative subtype does not express ER, PR or HER2 receptors. These two molecular subtypes tend to be associated with poorer prognostic outcomes than breast cancers with luminal subtypes which express high levels of hormonal receptors (ER and/or PR).

Traditionally, surgeons are often the patient's first contact within the oncology realm which allows them (surgeons) full control over the sequence of treatment offered. Though neoadjuvant therapy is the standard of care for locally advanced and inflammatory breast cancers, research has found that a substantial number of these patients proceed with primary surgery as the first-line treatment option. The reasons for this are varied or not clearly understood (Mamounas et al., 2016; Read, Flitcroft, Snook, Boyle, & Spillane, 2015). Therefore, it was important to determine what patient-, tumor- or facility-related factors were likely to motivate the surgeon to refer. Eligible patients should, at least, be offered the opportunity to discuss the option of neoadjuvant therapy with a medical oncologist.

Goals and Objectives

The primary goal of this practicum project was to evaluate whether surgeons were utilizing the referral process for patients with breast cancer to see a medical oncologist as intended, and in accordance with the recommendations of an Eastern Health BDSG evidence-based clinical practice guideline. The objectives of this practicum project were:

1. To establish the rates of surgeons' adherence to evidence-based clinical practice guidelines which recommend neoadjuvant therapy for the treatment of locally advanced and inflammatory breast cancers;
2. To determine which, if any, common factors or variables influence the surgeons' decision-making on the sequence of treatment modalities for patients newly diagnosed with locally advanced or inflammatory breast cancer; and

3. To demonstrate the advanced nursing practice (ANP) competencies of research and leadership required in this role as investigator of a program evaluation for clinical practice guideline adherence in the management of breast cancer.

Overview of Methods

The development of this evaluation project employed three different methods which included a comprehensive literature review, consultations/interviews with individuals having expertise in their fields, and a retrospective chart review. The initial intent in conducting this study was always to use an observational retrospective study design. Though retrospective chart reviews are an excellent pre-existing data source for research, they are also notorious for missing and incomplete data, lack of consistent reporting, and inability to verify certain reported information (Gregory & Radovinsky, 2012). These types of studies can also compromise the internal validity of a study by being particularly vulnerable to selection bias, misclassification bias, and information bias. In addition, the rigor of a study can be compromised by fallacies such as poor data collection techniques and lack of control for confounding factors. This study was conducted using strategies to control for bias and confounding while maintaining, and even strengthening, its rigor where possible.

The most integral components of any study's methodology are its study design, its sampling criteria, data collection process, and analysis of the study results. The methods utilized in developing these components for this evaluation project were a review of the research evidence which indicated the most common and effective study design for this type of project; consultations with experts to narrow the choice of inclusion and exclusion

criteria for the study; the use of effective tools to conduct a thorough and consistent collection of the necessary data; and an appropriate statistical analysis and interpretation of the study's final results.

Literature Review Summary

For this evaluation project, three separate literature searches were conducted in the databases of PubMed, Embase, CINAHL, and the Cochrane Library using MeSH terms and Boolean operators of "AND" and "OR" as best suited. The searches were limited to the time period of January 1, 2010 and January 31, 2018, inclusive. The searches also utilized additional filters or limiters which consisted of English language only, full-text and human-based studies. The keywords of the first of two literature searches consisted of "guideline adherence" (major heading), "cancer", "oncology", "audit", "research methods", and "breast" while the second search included all of the previous terms (except "audit" and "research methods") in addition to the terms "clinical audit", "medical audit", "quality of healthcare". The third search utilized the keywords of "surgeon clinical decision making", "neoadjuvant therapy", and "breast cancer". The first two searches yielded a total of 373 literature research articles, with 39 studies being chosen due to relevance to the topic at hand. Four of the studies focused on neoadjuvant therapy while the remaining 35 were general breast cancer-related studies, all of which measured adherence to a specific oncology clinical practice guideline. The third literature search, in addition to a hand search of the available studies, produced 11 research articles from which five were suitable for use in this evaluation. Refer to Appendix B for a copy of the literature review report.

The purpose of the first search had been to isolate research studies which measured adherence to a specific clinical practice guideline on the use of neoadjuvant therapy in the treatment of non-metastatic invasive breast cancer. The four neoadjuvant research studies were all rated as medium for quality as per the Public Health of Canada's (PHAC) critical appraisal tool kit (2014). Therefore, it was appropriate to consider emulating certain features of the methodology used in these research studies, such as type of study design, various patient/tumor/facility characteristics examined, and similarities in results for use in this evaluation project. Two of these research studies focused on the locally advanced breast cancer cohort only (Killelea et al., 2015; Spronk et al., 2017), one focused on an inflammatory breast cancer cohort only (Lin et al., 2017), while the remaining study included both the locally advanced and the inflammatory breast cancer cohorts (Mohiuddin et al., 2016).

Three of the four studies mentioned above were helpful in providing an expected rate for guideline adherence for both cohorts of interest. The range of surgeon adherence rates to neoadjuvant treatment guidelines for patients diagnosed with stage III locally advanced breast cancer was 44% to 79%, while the range of adherence was approximately 72% to 93% for those diagnosed with inflammatory breast cancer (Lin et al., 2017; Mohiuddin et al., 2016; Spronk et al., 2017). For all stage III locally advanced breast cancers, Mohiuddin and colleagues (2016) reported an adherence rate of 44% to 79% to a neoadjuvant guideline while Spronk and associates (2017) found a rate of 79%. For the inflammatory breast cancer cohort, Mohiuddin et al. identified an adherence rate of 93% while Lin and colleagues (2017) reported an adherence rate of 72% using tri-modality therapy (surgery, chemotherapy/endocrine therapy, radiation therapy). Killelea

and associates (2015) did not analyze their study results according to AJCC stage as did the others. Rather, these authors used the T stage and N status as the means by which to conduct their analysis and reported that 25% of the breast cancers referred for neoadjuvant treatment had a T2 tumor size (> 2cm but ≤ 5cm) while 58% had a T3 tumor size (> 5cm). Killelea et al. found that overall, 16.7% of all patients with T3 or smaller tumors who were categorized as having locally advanced breast cancer (either before or after definitive surgery) received neoadjuvant therapy.

Three of these studies were American and the results of all three found an increase in utilization of guideline-recommended therapy over the study period (Killelea et al., 2015; Lin et al., 2017; Mohiuddin et al., 2016). Killelea and associates found approximately a 7% increase in guideline adherence while Lin and colleagues found an 8% increase. Mohiuddin et al. used an adjusted risk ratio of 1.20 with a 95% CI (1.15-1.25) to support a modestly higher rate of neoadjuvant therapy utilization over the timespan of this study. The remaining study was of Dutch origin which reported no change at all over the period of the study (Spronk et al., 2017). The country of origin of the study has often been of importance to the Canadian oncology community, as there is a general understanding that the patterns of oncology treatment in Canada are most closely aligned with that of the United States, as compared to European countries. The type of facility where patients received treatment in these studies was categorized in terms of whether the facility was academically or university-affiliated, a teaching or comprehensive community hospital, or a general hospital. The results of two of these studies suggested that patients with locally advanced disease who received treatment at academically-affiliated healthcare centers were statistically more likely to receive

neoadjuvant therapy compared to general hospitals (Mohiuddin et al., 2016; Spronk et al., 2017).

During the literature search, it became apparent that there was a lack of research evidence available on the topic of clinical practice guideline adherence to neoadjuvant therapy with a result of only four research studies being found. The additional 35 studies had been chosen to obtain more information on the assessment of guideline adherence in other general breast cancer-related studies. All 39 studies utilized a retrospective cohort research design and measured guideline adherence over a pre-determined period of time. This was yet another strong justification for choosing a retrospective study design for use in this evaluation project. The 35 general studies included a variety of breast cancer-related topics such as breast cancer treatment and the elderly, survival using first-line adjuvant treatment regimens, and the survival outcomes between molecular subtypes. The results highlighted from these topics indicated that the rate of guideline adherent treatment decreased with advanced age; lowered survival outcomes when deviations occurred in the recommended first-line treatment choice; and lowered survival outcomes for those having triple negative and HER2 positive breast cancers whose treatment deviated from the recommended first-line treatment choice. All 39 studies were critically appraised using the Public Health Agency of Canada Critical Appraisal Tool Kit (2014). The majority were given a medium-quality rating and three studies received a low-quality rating.

Some of these studies were helpful in outlining aspects of the study design related to the inclusion and exclusion criteria, use of age stratification, the study time period of choice, and the selection of some variables of interest. Most importantly, these studies

were helpful in highlighting important strategies to aid in reducing the threat to the internal validity of a research study. One such strategy involved availing of the services of a cancer registrar in helping to minimize the risk of selection bias, misclassification bias and information bias which had often been inherent in several of these retrospective studies. These studies were also helpful in pointing out some disadvantages encountered in performing retrospective studies such as using data extractors unfamiliar with oncology data collection as well as inconsistent data collection results when the services of more than one data collector are being used. Having one investigator, with extensive breast cancer experience, who was solely responsible for data collection and able to ensure data accuracy was a distinct advantage in helping to control for misclassification bias. Another strategy of note was the use of a subgroup analysis to investigate multiple independent variables in a limited, stratified manner which was useful in controlling for the risk of confounding on the study outcomes.

The third search provided some additional insight into some of the most important patient/tumor/facility-related characteristics which the surgeon might take into consideration prior to making the decision to refer or to proceed to definitive surgery.

Consultations Summary

The consultation process involved face-to-face or telephone interviews with experts in the field of breast cancer, two medical oncologists and one general surgeon. In addition, a consultation had been arranged with the director of the provincial cancer registry and the ARIA computer clinical support person at the Dr. H. Bliss Murphy Cancer Center (DHBMCC), both of whom have specialty training and expertise within

their job classifications. A copy of the consultations report can be reviewed in Appendix C.

Medical Oncology

The two medical oncologists were interviewed face-to-face together, in order to form a consensus of opinion regarding the development of the eligibility criteria to be used for this study. Collaboration with the oncologists resulted in the development of the inclusion and exclusion criteria for the study population of two cohorts of patient cases according to diagnosis, locally advanced breast cancer and inflammatory breast cancer. Since the Eastern Health BDSG neoadjuvant guideline was disseminated in 2014, it was decided to stratify each cohort into groups according to a pre-guideline study year and a post-guideline study year in order to measure adherence.

Cancer Registry/ARIA Computer Support

The interview with the director of the NL Cancer Registry was instrumental in narrowing the choice of study years to that of 2013 and 2016 to reflect the pre- and post-guideline dissemination time periods. A written request was submitted, and upon meeting, the director provided an explanation of what types of data could be expected to be received from the cancer registry database. As a cancer registry, not all the data of interest were available through this database. Therefore, any data not available from the cancer registry database was to be collected by hand through a retrospective individual chart review.

The consultation with the director of the cancer registry was also helpful in explaining the changes that had taken place with the computer technology systems during the study's time period. A new paperless electronic health record known as the ARIA

computer system had been introduced in 2014, which simplified the chart review process for the 2016 post-guideline dissemination time period. ARIA provides access to the surgical, diagnostic, and pathological reports from the hospital MediTech computer system, as well as the oncological first assessment and progress notes. However, the chart review process for the pre-guideline dissemination period of 2013 proved to be more complicated. It involved retrieving data from the defunct computer system known as OPIS which housed the oncologists' first assessment and progress notes, the hospital MediTech computer system, and individual paper charts. The interview with the ARIA clinical support person was instrumental in obtaining the necessary computer training in order to retrieve the required data from that computer system.

General Surgery

The surgeon consultation was conducted as a telephone interview with a general surgeon. The interview questions and a list of patient- and tumor-related factors which had been compiled from the research literature were forwarded via email in advance of the interview. The surgeon indicated that tumor size ($\geq$ 5 cm); skin or chest wall involvement on imaging; presentation of clinical or imaging evidence of at least N2 (axillary lymph node level 2 disease); and/or a pathological diagnosis of inflammatory breast cancer were definite reasons to refer a patient for neoadjuvant consideration.

The surgeon suggested that extenuating factors may impact the decision to refer patients such as the general health of the patient and the presence of pre-existing co-morbidities. Frailty and/or the presence of cardiac, renal, and/or vascular insufficiencies are often grounds for which the surgeon would proceed with primary surgery. Consequently, the surgeon would be aware that these health limitations were likely to

prohibit the use of first-line pharmaceutical therapies with potentially cardiotoxic or thrombus-inducing effects. Age was also considered important since breast cancer in younger patients tends to be of a more aggressive nature than older patients, while general health status was more important in the elderly. However, the presence of frailty is also more frequent in the elderly population ≥75 years.

While discussing other tumor-related characteristics which may affect the decision-making process, the surgeon recognized tumor grade (poorly differentiated/grade 3), histology (such as apocrine, metaplastic) and the presence of bilateral or multi-focal and/or multi-centric disease as additional incentives for neoadjuvant referral. The surgeon also highlighted the impact of molecular subtyping and the need for testing on all needle core biopsy specimens. This would permit the surgeon to have prior knowledge of the molecular subtype information so that more cases of locally advanced HER2 positive and triple negative breast cancer can be referred for neoadjuvant therapy.

The previously mentioned patient demographics and tumor characteristics as described by the surgeon lent credibility to these specific factors as the optimal choices for investigation in this study. Some of these data were available from the Cancer Registry database however, the remaining required a thorough paper and computer chart review for both study years to complete the data collection.

Chart Review Summary

A copy of the chart review report has been included in Appendix D. The chart review process took place at the DHBMCC in St. John's. Though the Cancer Care Program has a provincial focus, the Cancer Center, itself, comes under the direction of the Regional Eastern Health Care Board. The program director of the NL Cancer Care

Program granted permission to the investigator to conduct this study with access to patient medical information as well as permission to request patient data from the NL Cancer Registry. The NL Health Research Ethics Authority (HREA) website provides a tool to help study investigators determine whether the intent of their study is either research or a quality assurance initiative. The tool was completed by the investigator and the results indicated that this project was a program evaluation initiative, and therefore exempt from HREA review and approval.

Sample

The two groups which comprise the sample population for this study were those patients who had been diagnosed with locally advanced or inflammatory breast cancer, during the pre-guideline dissemination year of 2013 and the post-guideline dissemination year of 2016. The eligibility criteria for those with invasive inflammatory breast cancer were the clinical presentation and a skin biopsy which provided pathological confirmation of diagnosis. The eligibility criteria for invasive locally advanced breast cancer consisted of having at least one or more of the following three characteristics:

- Tumor size > 5cm; and/or
- Presence of clinically palpable, or radiological imaging of, ipsilateral axillary lymph nodes or ipsilateral internal mammary nodes which is categorized of at least level II lymph nodes (N2) according to the AJCC staging manual (Edge et al., 2010); and/or
- Categorized as having AJCC breast cancer stages of either IIB (T3 N0 M0 only) or any stage III.

The exclusion criteria for both cohorts included metastatic disease at diagnosis, male breast cancers, or AJCC stages of breast cancer other than those listed in the eligibility criteria. In addition, the sample population was restricted to only those patients who had received at least two of the three primary treatment modalities of surgery, chemotherapy/endocrine therapy, and radiation therapy. For further clarification, the AJCC breast cancer staging guide can be found in Appendix A. Each patient case was categorized as having the outcome of being “referred” or “not referred” to the medical oncology discipline as indicated, in order to capture the referral rate (and calculate its corresponding proportion or percentage) for the cohort according to the year of study and diagnosis.

Methods

Upon receiving the written request, the director of the cancer registry performed the search for all newly diagnosed breast cancer patients for study years 2013 and 2016. Four data sources were accessed for the 2013 study year including the cancer registry dataset, paper charts, OPIS computer system and the hospital Meditech computer system. Only three data sources were necessary for the 2016 study year which included the cancer registry dataset, the new paperless ARIA computer system, and the Meditech computer system. Table 1 provides a visual demonstration of the kind of data collected and where it was collected from according to the study year of interest. The initial list of independent variables was compiled from the information provided by the literature review and the surgeon consultation. However, it became apparent during the chart review process that changes to this list were warranted in order for it to align more closely with the availability of the data.

Table 1

Sources for Data Collection

Variable	**Pre-Implementation (2013)**				**Post-Implementation (2016)**		
	Cancer Registry	**Paper Chart**	**OPIS**	**Medi-Tech**	**Cancer Registry**	**ARIA**	**Medi Tech**
Patient age	X				X		
Year of diagnosis	X				X		
Clinical tumor (T) size	X				X		
Tumor histology		X	X	X		X	X
Tumor grade		X	X	X		X	X
Unilateral/ bilateral		X	X	X		X	X
Multifocal/ multicentric		X	X	X		X	X
Clinical nodal status (N)		X	X	X		X	X
Clinical/ pathological AJCC stage	X				X		
Estrogen/ progesterone receptor status	X				X		
HER2 receptor status	X				X		
Chest wall/skin involvement	X				X		
Facility location		X	X	X		X	X

A data collection tool was adapted from the literature for use in obtaining and recording the required data in an organized and efficient fashion (Gregory & Radovinsky,

2012). A corresponding data dictionary was developed which provided definitions of the necessary data and ensured that the correct data were being collected. The data collection tool was first used during a pilot test conducted by the investigator using the first 15 patient cases of the 2016 sample. The pilot test was beneficial in helping to define the term referral, recognizing the lack of consistent reporting by surgeons and the lack of provincial-wide synoptic pathology reporting, as well as aiding in finalizing the choice of independent variables for use in this evaluation project.

Two new Excel spreadsheets were developed to manage the eligible patient data for each calendar year of study provided by the cancer registry and the data collected from the chart review. The data was de-identified by removing all personal identification information such as patient name, MCP number and date of birth. Each patient case was then given an unrelated identification number to protect the patient's identity and personal health information.

A multivariable analysis had been planned for this evaluation project in order to determine whether an association existed between being referred and the various independent variables chosen for study. However, the final sample size was too small to allow for a multivariable analysis. Microsoft Excel 365 software for Windows 10 was used to perform the statistical analysis for this study. The 95% confidence intervals (CI) were calculated for the referral rates from both years of study.

Results

A total of 113 patient cases were identified in the 2013 dataset however, 66 did not meet the eligibility criteria. This left a final sample size of 47 cases which consisted of four inflammatory breast cases and 43 locally advanced breast cancers. In 2016, a total of

133 patient cases were identified with 79 cases which did not meet the eligibility criteria. This resulted in a final sample size of 54 cases having two inflammatory breast cancers and 52 locally advanced breast cancers. A discussion of the study results has been provided separately according to diagnosis.

Inflammatory Breast Cancer.

From the results provided, it was apparent that there were four cases of inflammatory breast cancer in 2013 and only two in 2016. Neoadjuvant referrals were sent to medical oncology for all six cases. Though the sample sizes for both study years were exceedingly small, the results signify that 100% of inflammatory breast cancers were referred appropriately by their surgeons. A 100% guideline adherence rate does exceed the range provided in the literature review of 72% and 93% for this cohort, which suggests that surgeons in this province exceeded the expected adherence rate, at least for these six patients, during the study period. Therefore, the remaining discussion will have emphasis on the analyses of the locally advanced breast cancer cohort only.

Locally Advanced Breast Cancer.

Table 2 summarizes the results of the neoadjuvant referral rates, in terms of numbers and proportions, for the locally advanced breast cancer cohort in this study. The results showed that only 23.3% (95% CI: 10.6%, 35.9%) in 2013 and 26.9% (95% CI: 14.9%, 39.0%) in 2016 of the locally advanced breast cancer cohort were referred for neoadjuvant therapy discussion with a medical oncologist. These results were in sharp contrast compared to the inflammatory breast cancer cohort results and were much lower than the guideline adherence rate determined for this patient group from the literature review of 44% to 79%.

Table 2

Number and Proportion of Patients Diagnosed with Locally Advanced Breast Cancer (LABC) in 2013 and 2016

	2013 N = 43		**Total n (%)**	**2016 N = 52**		**Total n (%)**
	Referred n (%)	**Not Referred n (%)**		**Referred n (%)**	**Not Referred n (%)**	
Locally Advanced Breast Cancer (LABC)	10 (23.3%)	33 (76.7%)	43 (100%)	14 (26.9%)	38 (73.1%)	52 (100%)

These results merited a closer look at the data to determine whether any subgroup of this cohort was apt to have clinical disease which would make them more likely to be referred than the others. As mentioned previously, a large tumor size (≥ 5cm) such as T3 and T4 tumors; and/or evidence of level II nodal disease such as N2; and/or an AJCC stage IIB (T3N0M0 only) or any stage III breast cancer are characteristics of locally advanced breast cancer. The extent of lymph node involvement cannot be reliably, clinically determined in many cases which precludes its use, as well as the use of AJCC staging which also requires information on nodal involvement. Given that clinical tumor size can often be measured by the surgeon on examination, or by imaging, and that the presence of a ≥ 5cm tumor which defines a locally advanced breast cancer should automatically warrant a neoadjuvant referral, the investigator believed it was reasonable to perform a sub-analysis on the T3/T4 subgroup.

Locally Advanced Breast Cancer (T3/T4).

The referral results of the sub-analysis have been summarized in Table 3 according to study year. There were twice as many T3 and T4 tumors diagnosed in 2016 (n = 18) than in 2013 (n = 9) with an actual referral rate of approximately 61% (95% CI: 38.6%, 83.6%) in 2016. This rate falls within the parameters of the range identified in the literature review of 44% to 79% for the locally advanced breast cancer patient group.

Table 3

Number and Proportion of Patients Diagnosed with T3 and T4 Locally Advanced Breast Cancer (LABC) in 2013 and 2016

T size of Breast Cancer	**2013 (T3 & T4) n = 43**		**Total n (%)**	**2016 (T3 & T4) n = 52**		**Total n (%)**
	Referred n (%)	**Not Referred n (%)**		**Referred n (%)**	**Not Referred n (%)**	
T3	5(55.6%)	3(33.3%)	9 (20.9%)	9(50.0%)	6(33.3%)	18 (34.6%)
T4	1(11.1%)	0(0)		2(11.1%)	1(5.6%)	
Total	6(66.7%)	3(33.3%)	n = 43 (100%)	11(61.1%)	7(38.9%)	n = 52 (100%)

However, nearly 40% of the population considered to be locally advanced did not receive a referral to the medical oncology discipline. In addition, the referral rate for T3/T4 tumors in 2013 was approximately 67% (95% CI: 35.9%, 97.5%) which was higher than the 2016 referral rate, despite a doubling of T3/T4 tumors diagnosed in 2016.

Analysis of the Patient/Tumor/Facility-related Factors (All LABC).

An analysis of the factors which may influence the surgeons' decision-making had been conducted to determine if any had affected the rate of neoadjuvant referrals for the

whole locally advanced breast cancer cohort. An analysis of only those factors which had demonstrated a sizable number of referrals or substantial differences between the years of interest have been summarized in Table 4. The numbers were very small for this analysis which prevented the investigator from drawing firm conclusions on the results. However, it was possible to identify some notable trends from the data.

The most common pathological findings in breast cancer include a ductal histology, unifocal tumors, and unilateral disease. This was reflected in the data of this study with higher numbers of patient cases having these tumor-related characteristics than any other in their respective categories. There was a slight increase in the referral rate in 2016 (32.1%) compared to 2013 (25%). Unifocal and unilateral breast cancers typically represent less aggressive tumors than others in these categories, such as multifocal and multifocal/multicentric or bilateral disease. However, the numbers for these latter characteristics were too small to definitely indicate a reason to refer. Therefore, unifocal and unilateral tumors were not considered to be indicators for referral.

Table 4

Patient/Tumor/Facility-related Variables of LABC by Year and Referral Status

Variables	**2013**		**2016**	
	Referred n (%)	**Not Referred n (%)**	**Referred n (%)**	**Not Referred n (%)**
Age Range (years)	**Median Age: 58 Range: 35 to 85**		**Median Age: 61.5 Range: 33 to 85**	
41 – 50	2(22.2%)	7(77.8%)	5(55.6%)	4(44.4%)
61 – 70	3(37.5%)	5(62.5%)	2(11.1%)	16(88.9%)

Variables	2013		2016	
Facility Type				
Large Urban (University-affiliated)	8(40.0%)	12(60.0%)	8(24.2%)	25(75.8%)
Clinical Tumor Size				
≤T2	4(11.8%)	26(88.2%)	3(8.8%)	27(91.2%)
T3/T4	6(66.7%)	3(33.3%)	11(61.1%)	7(38.9%)
Lymph Node Status				
Negative	1(7.1%)	13(92.9%)	0(0)	4(100%)
Positive	9(31.0%)	20(69.0%)	14(29.2%)	34(70.8%)
AJCC Stage (Clin/Path)				
Stage IIIA	6(23.1%)	20(76.9%)	10(31.3%)	22(68.8%)
Tumor Histology				
Ductal	7(25.0%)	21(75.0%)	9(32.1%)	19(67.9%)
Tumor Grade				
Grade 2	5(21.7%)	18(78.3%)	5(27.8%)	13(72.2%)
Grade 3	3(21.4%)	11(78.6%)	7(22.6%)	24(77.4%)
Molecular Subtype				
HER2 Positive	0(0)	1(100)	0(0)	3(100)
Triple Negative	4(33.3)	8(66.7)	7(53.8)	6(46.2)

Nevertheless, this analysis of the locally advanced breast cancer cohort and the various factors of influence according to referral rate and year did find some noteworthy trends in the data. Among these were:

- In 2016, a higher proportion (55.6%) of younger patient cases aged 41 to 50 years were referred compared to 2013 (22.2%);
- In 2016, despite a larger number of patient cases aged 61 to 70 years compared to 2013 (18 cases vs 8 case), a smaller proportion were referred (11.1% vs 37.5%), respectively;
- In 2016, despite a larger number of patient cases receiving definitive surgery at university-affiliated hospitals compared to 2013 (33 cases vs 20 cases), a smaller proportion were referred (24.2% vs 40%), respectively;
- The number of T3/T4 tumors were approximately one third of the number of tumors ≤ T2 in 2013 (9 cases vs 30 cases, respectively) and approximately one half in 2016 (18 cases vs 30 cases, respectively). However, T3/T4 tumors were substantially more likely to be referred in both 2013 and 2016 (66.7% vs 11.8%) (61.1% vs 8.8%), respectively;
- Nine cases (31%) and 14 cases (29%) with positive lymph node involvement were referred in 2013 and 2016, respectively. However, only one case in 2013 and no cases in 2016 were referred with negative lymph node involvement;
- A larger number of Stage IIIA breast cancers were diagnosed in 2016 compared to 2013 (32 cases vs 26 cases), with a slightly higher proportion referred in 2016 (31.3% vs 23.1%), respectively;

- Despite grade 3 tumors having the most aggressive nature, there was virtually no difference in referral rates between 2013 and 2016. However, there were slightly more referrals for cases with grade 2 tumors in 2016 (27.8%) compared to 2013 (21.7%); and
- Despite the small numbers of patient cases, it was evident that molecular subtype had some impact on referral rates. A higher proportion of triple negative cases were referred in 2016 compared to 2013 (53.8% vs 33.3%), respectively. However, neither of the four cases of HER2 positive in 2013 and 2016 had been referred for neoadjuvant consideration.

Analysis of the 2016 Patient/Tumor/Facility-related Factors (T3/T4 LABC).

This final analysis was conducted on those patient cases with locally advanced breast cancers having T3/T4 tumors for the study year of 2016 only. This analysis provided a closer look at the referral process in terms of the impact certain factors may have on the surgeons' decision-making in present day for those who should have routinely been offered a referral for neoadjuvant therapy. Once again, the numbers in this sample were too small to draw any firm conclusions overall. However, the investigator was able to identify certain interesting trends in the data. Table 5 provides a summary of only those factors which had illustrated a trend in the analysis results. These trends were:

- Of the five patient cases in the younger age group of 41 to 50 years, four were referred while the other was not;
- Of the nine patient cases who received definitive surgery in university-affiliated hospitals, six were referred and three were not;

- Of the 16 cases with positive lymph node involvement, 11 were referred and five were not;
- Seven of the 11 cases with AJCC Stage IIIA breast cancer were referred while four of the 11 were not, and all four patient cases with Stage IIIC breast cancer were referred; and
- Finally, six out of the seven patient cases with triple negative breast cancers were referred while one out of seven was not.

Table 5

Patient/Tumor/Facility-related Variables of Clinical T3/T4 Tumors of LABC by Referral Status for 2016

Variables	**Referred n = 11**	**Not Referred n = 7**
Age Range (in years)	**Median Age: 54 Range: 34 to 79**	**Median Age: 55 Range: 33 to 85**
41 – 50	4	1
Facility Type		
Large Urban (University-affiliated)	6	3
Lymph Node Status		
Positive	11	5
AJCC Stage (Clinical or Pathological)		
Stage IIIA	7	4
Stage IIIC	4	0
Molecular Subtype		
Triple Negative	6	1

Discussion

Surgeons in this province were 100% compliant with the recommendations of the Eastern Health BDSG neoadjuvant guideline regarding referral of patients with inflammatory breast cancer, at least with the six patients studied in 2013 and 2016. However, the locally advanced breast cancer referral rate data can be far more complicated to interpret. The definition and multiple tumor features of this cohort add to its complexity, thereby likely impacting the surgeons' interpretation of the guideline as well as the decision to refer. The initial referral rate results for all locally advanced breast cancers was approximately 23% (95% CI: 10.6%, 35.9%) in 2013, while the referral rate was approximately 27% (95% CI: 14.9%, 39.0%) in 2016. The confidence intervals for 2016 suggest that the true referral rate may be as low as 15% or as high as 39%. The referral rates, including the confidence interval values, for both study years were substantially lower than the rate range of 44% to 79% found in the literature review. Although the 2016 referral rate (27%) was slightly higher than the 2013 rate (23%), the consistent overlap of both confidence intervals suggests that there was little difference between these rates.

The results of the T3/T4 subset analysis found a referral rate of approximately 61% (95% CI: 38.6%, 83.6%) in 2016 and 67% (95% CI: 35.9%, 97.5%) in 2013. These results did align with the referral rate range found in the literature (44% to 79%). However, the confidence intervals for 2016 indicate that the true referral rate could be as low as 38% or as high as 84%. These confidence intervals are much wider for the T3/T4 subgroup than for the whole locally advanced breast cancer cohort and would require a much larger sample size to get a more accurate picture of the true referral rate for the

T3/T4 subgroup. Lastly, there was considerable overlap for the confidence intervals representing both years of study in the T3/T4 subgroup. As was true for the whole locally advanced breast cancer cohort, despite the finding of a higher referral rate in 2013 there really was little or no difference in the referral rates between 2013 and 2016. Regardless, the take-home message remains the same in that the referral rate for locally advanced breast cancer cohort requires improvement, especially for T3 and T4 tumors.

The sample sizes were small for each of the patient/tumor/facility-related factors which may affect decision-making, especially for the T3/T4 subgroup, making it difficult for firm conclusions to be drawn from the results. Nevertheless, some trends were noticeable which included younger patients, those who had surgeries performed at hospitals with university-affiliated programs, those diagnosed with positive lymph node involvement, Stage IIIA or IIIC, and/or triple negative disease which seemed to be more likely to be referred for consideration of neoadjuvant therapy.

With respect to guideline adherence for referrals of the locally advanced breast cancer cohort, it was readily apparent that there has been little or no change since the BDSG guideline was disseminated. These results appear to suggest that the guideline has had little or no effect on clinical practice. In Canada, as well as other developed countries, there has been a noted lack of compliance to clinical practice guidelines in healthcare (Gupta et al., 2016; Hall, Irish, Gregg, Groome, & Rohland, 2015). Physicians often claim time and unavailability of resources as reasons for incompliance, as well as the length, complexity and variety of choice that some guidelines provide (Vogel, 2011).

Recommendations

As a result of the evaluation, several underlying issues had been revealed concerning the referral program for neoadjuvant therapy as well as the clinical practice guideline development program. The referral rates indicate that in 2016, only 61% of all patients with locally advanced breast cancers who should indisputably have received a referral to the medical oncology discipline for a neoadjuvant therapy discussion, did so. Despite the 2016 referral rate being within the range identified in the literature, nearly 40% of patients with locally advanced breast cancer did not avail of the benefits of neoadjuvant therapy. Some recommendations which could be helpful in efforts to increase the rate of patient referrals by surgeons and improve patient outcomes are:

I. Provide a written report of the evaluation project's results in an executive summary in order to inform the administrative leads of the findings and issues brought to light by this study. A copy of the executive summary has been provided in Appendix E. Feedback and advice from the administrative body on how best to initiate change within the system would be welcome and of particular importance in initiating it.

II. Present the results in a future meeting of the Eastern Health BDSG, using a PowerPoint presentation. A discussion will be encouraged to determine what measures can be taken within the necessary departments to improve the process and allow more consistent use of neoadjuvant therapy for those patients who would benefit the most from this treatment strategy. Some suggestions are standardizing receptor testing on needle core biopsies to determine molecular subtypes earlier; continue advocating for synoptic reporting for radiology

departments and pathology labs all across the province; advocate for standardized or synoptic reporting of the decision-making process by the surgeon; and encouragement of more collaborative efforts between surgeons and oncologists.

III. Encourage the BDSG to implement more professional development initiatives to provide education regarding the interpretation of research into clinical practice, such as local conferences or workshops aimed at surgeons and family physicians; use of team-building strategies to promote a team approach which may be helpful in boosting the consistent use of clearly defined guidelines for neoadjuvant therapy referrals.

The process for deciding which patients to refer for neoadjuvant consideration can be complicated and dependent upon a host of elements which are not always easily defined. Clinical practice guidelines can be an important resource for surgeons to quickly and easily determine the best treatment option to pursue for patients in varying circumstances. However, many surgeons have complained about the complexity, lengthiness, and the time-consuming effort needed in using clinical practice guidelines. The following recommendations have been provided as a means by which the development, dissemination, and utilization of the BDSG clinical practice guidelines can be improved. They are:

IV. Carry out a survey to determine whether the surgeons of NL know of the existence of the BDSG clinical practice guidelines, where to find them, and are they utilizing them. A summary of the evaluation project's results can be provided in an effort to engage the surgeons' interest. Also, a survey provides

surgeons with the opportunity to voice their opinions on the content of the guideline and any issues they may have with it.

V. Change the future approach to clinical practice guideline development in order to incorporate strategies which will help meet the needs of the surgeon, such as creating a shorter version of the guideline and the use of treatment decision algorithms, such as those located in the appendices of the chart review report and the executive summary in Appendix D and E of this report. The future goal would be to make the Eastern Health BDSG guidelines more user-friendly and simpler to use.

VI. Revisit the dissemination practices for new BDSG guidelines to surgeons and family physicians. Improving the process, requesting feedback, and following up on the information provided may be useful strategies in engaging physicians to bring about change.

VII. Begin the process of incorporating quality indicators in future clinical practice guidelines to establish outcome measurement as a means of determining the effectiveness of the guideline and whether quality improvement actions are necessary.

Next Steps

The next steps are to share the results and recommendations of this evaluation project with the Program Director of the Cancer Care Program, the chief of the medical oncology discipline, the chair of the Eastern Health BDSG, and then the BDSG itself. A written executive summary will be provided for the organizational management listed above. It will summarize the objectives of the evaluation project, an overview of the

methods, and the key results with a focus on recommendations to help address the identified issues. Later, a PowerPoint presentation will be provided with a similar outline for the BDSG membership at a regularly scheduled monthly meeting.

Action must be taken to follow up on and incorporate the recommendations provided in this project in an effort to facilitate, increase, and improve the use of neoadjuvant referrals for the appropriate study populations. In addition, work needs to begin on the use of quality indicators in the development of new clinical practice guidelines for quality improvement purposes. Future evaluations of other pre-existing guidelines, developed by the BDSG or other tumor-site groups, can be implemented by using this evaluation as a model and adapting its methods as necessary in order to measure adherence and improve patient and healthcare system outcomes.

Advanced Nursing Practice (ANP) Competencies

Advanced practice nurses possess extensive clinical experience, leadership qualities, knowledge about the inner mechanisms of their respective healthcare organizations, as well as the higher education which can bind these attributes into an astounding force for change in the healthcare realm. These nurses have been recognized by the Canadian Nurses Association (CNA) as being strategically poised to take on the role for initiating guidance and support in order to improve outcomes for patients, the institution, and the healthcare system as a whole. The Association of Registered Nurses of NL (ARNNL) has also recognized the importance of clinical nurse specialists who possess these attributes and use their knowledge and skills as a means to improve the consistency of healthcare delivery by using research evidence-based practice (2013). The development of clinical practice guidelines in various healthcare fields, including

oncology, has frequently been the domain of graduate-level nurses in this country and this is likely to continue. The CNA has articulated four competencies which are expected of an advanced nursing practice, and categorized as clinical, research, leadership, and consultation and collaboration (2014). Two of these categories have been demonstrated during the conduct of this evaluation project, namely research and leadership.

In this evaluation project, the demonstration of the research competency for advanced nursing practice involved employing research methodology in the project's performance and the utilization of research. Though this project was not a research study, the evaluation process required the use of some research methodology to carry it out. Some of these research methods included the utilization of descriptive objective measures, choosing and employing a retrospective study design, conducting semi-structured interviews, using a data collection tool and data dictionary, as well as utilizing the most appropriate statistical analysis for the data.

Research utilization was evident in the use of a comprehensive literature review, and the critical appraisal of the available literature, to identify and assimilate the most appropriate and best quality research evidence on the practice of neoadjuvant therapy and guideline adherence. Research utilization was also evident from the consultations process which helped define the populations of interest, the eligibility criteria, the periods of study and the data sources. The evidence from both the literature review and the consultations informed the chart review process which utilized research to carry out the evaluation project as well as to collect and analyze the results. The knowledge gained from the evidence collected on all three of these processes (literature review,

consultations, and chart review) were necessary to inform the recommendations offered for this project as a means to improve patient outcomes.

As the NL representative on a national oncology Guideline Facilitators group, the investigator has already assumed a leadership role in the field of clinical practice guideline development. However, having to assume a leadership role in evaluating the neoadjuvant referral process within the Cancer Care Program has been a new experience for this investigator. The experience has provided an opportunity to identify issues within the healthcare system which need attention and to develop appropriate strategies that can be implemented in an effort to address the areas of concern. One example of an organizational/system gap or problem identified by the investigator was the need to modify or transform the neoadjuvant clinical practice guideline into a shorter and more user-friendly version. In response to this identified need, the investigator developed decision-making algorithms to assist physicians in determining appropriate treatment sequencing to guide the care of patients with breast cancer. Developing recommendations and advocating for their use are valuable approaches to take in order to improve the delivery of evidence-based care which fundamentally demonstrate leadership capabilities.

Conclusion

The utilization of a comprehensive literature review and the consultations with specific individuals of expertise provided an important foundation for this evaluation project which informed its methodology and choice of patient/tumor/facility-related factors to study. The knowledge gained from this phase of the project was also crucial in informing the chart review process as well as the analysis and interpretation of the data.

The data analysis highlighted the complexity of the decision-making process meant to determine what patients were candidates for neoadjuvant referral. It became obvious that the preliminary data did not tell the full story regarding referral rates for neoadjuvant discussion in this province. This advanced the need for a deeper examination of the data which, in combination with the knowledge and extensive clinical experience, was sufficient to emphasize that there were other dynamics at play which were skewing the results.

The results of the T3 and T4 subgroup proved to be a better representation of the state of neoadjuvant referral rates in NL compared to that of the entire local advanced breast cancer group. Nevertheless, the results still suggest that approximately 40% of the patients are not being referred to the medical oncology discipline for a discussion of regarding neoadjuvant treatment. There is obvious room for improvement which will require the collaboration of the various key stakeholders to implement policies and strategies to create change which moves the Cancer Care Program along the path of achieving the best patient outcomes for those diagnosed with breast cancer in the province of NL.

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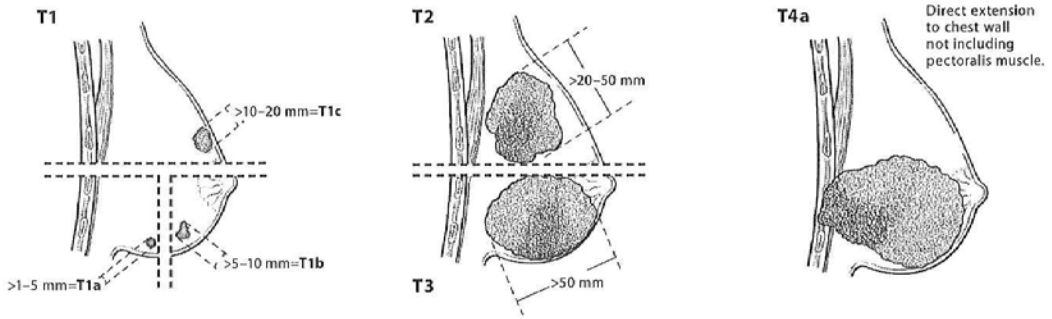
Appendix A: AJCC Breast Cancer Staging

American Joint Committee on Cancer

Breast Cancer Staging

7th EDITION



Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Tis (DCIS) Ductal carcinoma in situ

Tis (LCIS) Lobular carcinoma in situ

Tis (Paget's) Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted

T1 Tumor ≤ 20 mm in greatest dimension

T1mi Tumor ≤ 1 mm in greatest dimension

T1a Tumor > 1 mm but ≤ 5 mm in greatest dimension

T1b Tumor > 5 mm but ≤ 10 mm in greatest dimension

T1c Tumor > 10 mm but ≤ 20 mm in greatest dimension

T2 Tumor > 20 mm but ≤ 50 mm in greatest dimension

T3 Tumor > 50 mm in greatest dimension

T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4

T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion

T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma

T4c Both T4a and T4b

T4d Inflammatory carcinoma (see "Rules for Classification")

Distant Metastases (M)

M0 No clinical or radiographic evidence of distant metastases

cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes

* T1 includes T1mi.
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
+ M0 includes M0(i+).
# The designation pM0 is not valid; any M0 should be clinical.
^ If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
~ Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
~ Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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Breast Cancer Staging

7th EDITION

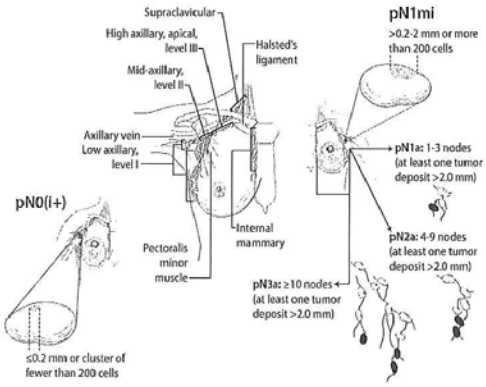
Regional Lymph Nodes (N)

CLINICAL

- NX Regional lymph nodes cannot be assessed (for example, previously removed)
- N0 No regional lymph node metastases
- N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
- N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- N3a Metastases in ipsilateral infraclavicular lymph node(s)
- N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- N3c Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.



PATHOLOGIC (PN)*

- pNX Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
- pN0 No regional lymph node metastasis identified histologically

  Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
- pN0(i–) No regional lymph node metastases histologically, negative IHC
- pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
- pN0(mol–) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
- pN0(mol+) Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
- pN1 Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
- pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
- pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
- pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
- pN2 Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- pN2a Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
- pN2b Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
- pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
- pN3b Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN3c Metastases in ipsilateral supraclavicular lymph nodes

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

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Appendix B: Literature Review Report

ADHERENCE TO AN ONCOLOGY CLINICAL

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Memorial University of Newfoundland

April 24, 2018

In accordance with one of the main objectives of the practicum proposal, it was necessary to gather knowledge on how to evaluate whether adherence exists to the Eastern Health Breast Disease Site Group's (BDSG) "*Neoadjuvant Treatment of Primary Breast Cancer"* evidence-based clinical practice guideline (CPG) in Newfoundland and Labrador (NL). One method to compile this knowledge would require a thorough search and review of the published literature. This would allow a close evaluation of the experiences of other researchers who have explored guideline adherence in a variety of other management- and treatment-related breast cancer (BC) topics. This literature summary describes the complete process of how the literature search was carried out, how the decisions were made regarding the choice of the studies to be used, and an in-depth appraisal of the findings to determine the appropriate means by which to evaluate how surgeons decide which patents should be referred to medical oncology for neoadjuvant therapy consideration.

Literature Search Methods

To begin this process, three important questions must be asked and answered to help establish the foundational basis for not only this literature review but also for this practicum project, itself. The questions were:

1. Is adherence to guidelines an issue in the clinical practice of breast cancer management and treatment?
2. What methods and/or measures have been used in other research studies to determine guideline-adherence in the management and treatment breast cancer?

3. What factors affect the deliverance of guideline-adherent care in the clinical practice of breast cancer?

In order to answer these questions, a strategy needed to be devised which would provide a comprehensive review of the available literature. The aid of a librarian was enlisted at the Health Sciences Library, located in the Health Sciences Centre, regarding the appropriate choice of key terms to use in the search. The key words chosen were MeSH terms with broad headings intended to capture the largest number of available research possible. The keywords included “guideline adherence” (as a major heading), “cancer OR oncology”, “audit OR research methods”, and “breast”, with Boolean operators “AND” and ‘OR” as best suited. Using these key words, additional filters or limiters of English language only, full-text and human-based studies were applied. The search was carried out in both nursing and medical databases included PubMed, Embase, CINAHL, and the Cochrane Library from January 1, 2010 until January 31, 2018. This search yielded 152 research articles from which only three research studies were directly related to the neoadjuvant treatment of invasive breast cancer.

A second search was conducted using the MeSH terms “guideline adherence (major)”, “cancer OR oncology”, “clinical audit OR medical audit OR quality of health care”, and “breast”. This second search was performed in an attempt to capture additional neoadjuvant research studies. Again, the filters used were English language only, full-text and human-based studies, with the search carried out in the same nursing and medical databases as the first search, with the same time line. This second search yielded 294 for a total of 446 literature articles, adding only one neoadjuvant research study for a result of four (Killelea et al., 2015; Lin et al., 2017; Mohiuddin et al., 2016; Spronk et al., 2017).

Clearly, four neoadjuvant research studies were too few studies in which to perform an appropriate literature review on guideline adherence effectively. Hence the decision was made to include research studies from both previous searches, which had measured guideline adherence with a focus on breast cancer management or treatment, other than the use of neoadjuvant therapy. This approach provided an opportunity to garner additional knowledge regarding other breast cancer-related topics on guideline adherence. This resulted in a retrieval of thirty-nine (39) eligible studies, which were deemed appropriate for the evaluation of guideline adherent clinical practice in the management of breast cancer.

In addition, a third search was performed to evaluate what factors influenced the surgeon's decision to refer patients with breast cancer to the medical oncology discipline for consideration of neoadjuvant therapy. The Mesh terms of "surgeon clinical decision making", "neoadjuvant therapy", and "breast cancer" and the Boolean operator "AND", with filters of English language only, full-text, and human studies were used to search the PubMed and Embase databases, over the last ten years. This search resulted in seven research articles. An additional hand search of the reference lists of various literature review articles revealed four additional articles on this topic. From the resulting 11 articles, only five were useful in the evaluation of factors affecting neoadjuvant referral to medical oncology.

Inclusion and Exclusion Criteria

The original inclusion and exclusion criteria were meant to closely reflect the inclusion/exclusion criteria to be utilized in the proposed study. However, since only four research articles were found which related to the topic chosen, the search parameters were

adjusted to include all research studies of a breast cancer-related topic which attempted to measure guideline adherence. The inclusion criteria were for all studies with a primary breast cancer focus, which:

1. Measured adherence to a specified clinical practice guideline developed by a credible organization, or for a national/provincial purpose;
2. Comprised an adult female population only;
3. Conducted at a single institution or across multiple institutions or centers;
4. Used a retrospective cohort design; and
5. Data extracted from cancer/tumor registries and/or patient medical records and/or breast cancer-specific databases only.

The exclusion criteria were studies with:

1. A metastatic breast cancer cohort;
2. Male breast cancers;
3. A mixture of primary cancers including breast (e.g., lung and bowel cancers); and/or
4. Embedded quality indicators, use of care pathways, and post-quality improvement measures.

The inclusion criteria were meant to reflect the methodology which had been agreed upon by the Eastern Health BDSG and which was best suited for the purposes of this proposed study, in terms of design, data source, and the specific guideline of use. Since most clinical trials include only female participants to increase the homogeneity of the cohort, this tactic was also utilized for this project. The inclusion of multicenter studies allows for more generalizable findings that may be applicable to what could be expected

from other centers within the westernized world. Though the findings of single institution studies may be more restrictive for comparison purposes, if the methodology was sound then the study was included.

The exclusion criteria were defined to reduce the focus of the literature search to an earlier stage of breast cancer cohort having a curative potential, eliminating those with end-stage disease. Most breast cancer studies will exclude the rare cases of male breast cancer to prevent confounding, and therefore were excluded from the literature search. Though several research studies investigated cohorts from a mixture of different disease sites (e.g., lung, bowel) which included breast cancer, these were excluded in favor of studies which had a primary focus of breast cancer only. Studies which had employed quality improvement measures were also excluded, since this can affect how data is extracted and consolidated potentially introducing selection bias. Since the intent of this project is evaluation only, its utilization is meant as a pre-quality improvement initiative. In addition, none of the Eastern Health BDSG CPGs have embedded quality or performance indicators and therefore these may not be helpful in explaining the findings of this project. Finally, studies which evaluated post-quality improvement measures (other than the development and publication of a clinical practice guideline) were excluded to prevent confounding of the evidence. A glossary has been provided of the common abbreviations used in the specialty of oncology and are tabled in Table 1 of the appendix.

Results

The four neoadjuvant research studies consisted of three American studies and one Dutch (Killelea et al., 2015; Lin et al., 2017; Mohiuddin et al., 2016; Spronk et al., 2017). All three of the American studies used the recommendations of the National

Comprehensive Cancer Network (NCCN) Breast Cancer guideline as the standard of care while the Dutch study referred to the recommendations of a national breast cancer guideline. All three of the American studies used the National Cancer Database (NCDB) from which to collect their data while the authors of the Dutch study selected data from a national multidisciplinary registry known as the NABON Breast Cancer Audit (NBCA).

The remaining 35 breast cancer research studies chosen demonstrated an international representation comprised of 13 from the United States, 11 from Germany, two from Australia/New Zealand while five were Dutch, two were Canadian, one British and one French. It should be noted that various countries have access to different databases from which researchers can extract the necessary breast cancer data to analyze their subject of interest. The American studies have the largest number of cancer- or breast cancer-specific database resource options from which to extract data. The most common sources are the NCDB, which despite its national title comprises only 70-80% of all cancer cases in the United States, and the Surveillance, Epidemiology, and End Results (SEER) data, covering approximately 26% of the cancers in the population (Hattangadi, Taback, Neville, Harris, & Punglia, 2012; Killelea et al., 2015; Mohiuddin et al., 2016).

Though the NCDB is the largest cancer database in the U.S, it has been criticized because it collects data only from those hospitals whose cancer programs have been accredited by the American College of Surgeons' Commission on Cancer (Wu et al., 2012). The argument raised is that study results are often only a reflection of accredited hospitals and not necessarily those of all hospitals across the United States, especially those in smaller rural areas. Other American studies used in this review extracted their

data from regional or state cancer registries, while two studies used the database of hospitals affiliated with NCCN.

Most of the remaining studies, from other countries other than the United States, obtained their data from either a national or regional cancer/tumor registry (often supplemented by patient data from appropriate healthcare/hospital facilities), or from breast cancer-specific databases created for the purposes of research. However, two studies, one French and one Canadian, obtained patient data alone from either regional or institutional healthcare systems.

It became apparent that certain countries, such as Germany, the Netherlands, and the United States, have committed to publishing their efforts to achieve national standards of care in the guideline-adherence of the treatment and management of breast cancer. This was reflected in the fact that 33 of the 39 studies had been conducted in these three countries alone. The NCCN and the American Society of Clinical Oncology (ASCO) are large national organizations in the United States, which develop evidence-based breast cancer treatment guidelines, while both Germany and the Netherlands have developed their own national guidelines. Unlike these countries, Canada does not have a national oncology CPG development organization, rather the onus falls upon provincial oncology programs to implement CPGs (either de novo or through adoption/adaptation) suitable for use for cancer management, within each unique provincial setting. Some of the prominent provincial oncology guideline developers in Canada include such organizations as Cancer Care Ontario and the B.C. Cancer Agency. The NL Cancer Care Program within Eastern Health has been developing guidelines for ten years, and the “Neoadjuvant Treatment of Primary Breast Cancer” CPG has been in circulation since 2014.

All 39 of the studies were quantitative, analytical and of similar design, specifically that of an observational retrospective nature. Though each study had a breast cancer focus and the primary aim was whether clinical practice adhered to the recommendations of a specific guideline, the topics themselves varied substantially. Therefore, to simplify the interpretation of the results the studies were grouped according to topic and tabled together in the appendix. The grouped studies and corresponding table were neoadjuvant therapy (Table 2), adjuvant therapy (Table 3), breast conserving therapy (Table 4), radiation therapy (Table 5), breast cancer treatment and the elderly (Table 6), molecular profiling (Table 7), staging investigations (Table 8), tumor characteristics (Table 9), and axillary evaluation (Table 10). Three single studies concerning immediate breast reconstruction (Table 11), genetic counselling/testing (Table 12), and follow-up (Table 13) are located in the appendix.

Each study was tabled with information on the authors' names, country of origin, study design, and the main objective of the study. The sample size and methodology were recorded along with the study's inclusion and exclusion criteria, the specific clinical practice guideline being tested for adherence, and the primary endpoints of the study. The key results and findings were listed, followed by the strengths and limitations of the study. Each study was also appraised, and the evidence graded using the Public Health of Canada's (PHAC) critical appraisal tool kit (2014) resulting in a judgement being awarded on the strength of the study design, the quality of the study, and whether the evidence was direct or extrapolated were given for each study. All the studies were of a similar retrospective cohort design and the critical appraisal tool kit rates this design as moderate. A prospective randomized controlled trial, despite being considered a strong

study design, is not always an ethical choice for some research questions. Therefore, the retrospective cohort design is an appropriate choice when the intervention has occurred naturally without control by the investigator (Yang, Chang & Chung, 2012).

A potential for sampling or selection bias will always exist with retrospective cohort studies of this nature since random sampling cannot be used. The findings of studies using large national databases are generalizable only if the study population is similar to the population to which one wants to generalize. Having similar eligibility criteria will facilitate comparison across studies. The risk of misclassification bias or coding errors is also another concern for retrospective cohort studies and were often the deciding factor between being awarded a strong and a medium quality rating for the chosen studies of this literature summary. Information bias can also be an issue with retrospective studies due to lack of blinding and lack of training in appropriate data collection methods. The higher the risk of misclassification and information biases, the higher the likelihood of a real threat to the internal validity of the study. The ratings for quality of the 39 studies varied from low to medium, depending on the measures taken by the investigators of these studies to control for internal and external validity threats.

The methodology of the neoadjuvant studies will be instrumental in directing much of how this proposed study will be carried out. However, the methodology of the remaining study groups can also offer important insights into how to conduct or improve other aspects of this proposed study not addressed by the neoadjuvant studies. Each of the following group of studies will be reviewed for their general findings and any potential suggestions for use for this practicum project.

Neoadjuvant Therapy Studies

Findings. The four studies concerning the use of neoadjuvant therapy were submitted in Table 2 of the appendix. All four of the neoadjuvant guideline-adherent studies differed in purpose, though all investigated the rates of neoadjuvant therapy use as an outcome of interest. Lin and colleagues (2017) focused on the treatment of inflammatory breast cancer only while Killelea et al. (2015) studied the rates of breast conserving surgery after neoadjuvant therapy. Both Mohiuddin et al. (2016) and Spronk et al. (2017) investigated the practice patterns in neoadjuvant use, though Mohiuddin and colleagues chose a locally advanced and borderline-lumpectomy population cohort while Spronk et al. concentrated solely on the locally advanced population. All three American neoadjuvant studies found that neoadjuvant therapy use had increased over each study's timespan (Killelea et al., 2015; Lin et al., 2017; Mohiuddin et al., 2016). As per the American Joint Committee on Cancer staging manual (7^{th} ed.), Mohiuddin and colleagues (2016) described an 44% utilization of neoadjuvant therapy for stage IIIA invasive breast cancer, 79% in T4 tumors of stage IIIB, 53% for stage IIICs, and 93% for use in inflammatory breast cancer. In comparison, the Dutch neoadjuvant study reported a high rate of 79% for neoadjuvant therapy for all stage IIIs with no significant change over its timespan (Spronk et al., 2017).

All four of these studies also found a wide variation for neoadjuvant therapy use across cancer facility type or location. Each of the four studies compared the type of facility, where the treatment had been administered, and labeled them according to whether they were academically affiliated with a university, a teaching or comprehensive community cancer center, or a general community hospital. Two studies found that 63.4%

to 88% of patients with stage III invasive breast cancer received neoadjuvant chemotherapy and/or endocrine therapy at an academic-affiliated center, while 52.6% to 79% at a teaching/comprehensive center, and 49.1% to 75% at a general community hospital (Mohiuddin et al., 2016; Spronk et al., 2017). Killelea and colleagues (2015) found that 19% of patients with stage I to III invasive breast cancer received neoadjuvant therapy at an academic-affiliated center while only 13% did so at general community hospitals. All studies, except for Lin and colleagues (2017), were able to show a statistically significant association between treatment and facility type. In contrast, Lin and colleagues (2017) found that facility location was statistically significant for those who received guideline recommended tri-modality therapy (i.e., neoadjuvant chemotherapy, modified radical mastectomy, and post-mastectomy radiation therapy) for the treatment of inflammatory breast cancer. The authors suggested that this was probably due to the high variation in tri-modality therapy seen in the comprehensive community centers and the academic/research hospitals over the course of the study. The results of this American study found those who lived in the Midwest were more likely to receive tri-modality therapy (77.2%) than those living in the South (66.5%).

Quality and Insights. The quality rating for all four neoadjuvant studies was medium which is sufficient to justify mirroring certain components of their methodology in the conduct of this proposed study. It was apparent from these neoadjuvant studies that missing data is likely a common issue with large databases. Killelea and colleagues (2015) admitted that 26% of their study population were missing important clinical staging information as per the American Joint Committee on Cancer (AJCC) staging manual (7^{th} ed.), while Mohiuddin et al. (2016) also excluded cases with incomplete

AJCC staging data. Patient cases were also excluded when no primary surgery was performed in order to reduce heterogeneity in the sample (Lin et al., 2017; Mohiuddin et al., 2016). Spronk and colleagues (2017) also excluded cases with unknown treatment sequencing. Excluding cases with incomplete clinical AJCC staging or unknown treatment sequencing is a necessary strategy in this proposed study since clinical staging and treatment sequencing are focal to the eligibility criteria for neoadjuvant therapy. In addition, unlike the study by Mohiuddin and colleagues, this proposed study is focused primarily on who gets referred for neoadjuvant therapy, not whether patients were able to undergo primary surgery after its completion. Therefore, cases will not be excluded from this proposed study for that reason alone.

Each of the four studies used multiple stratification measures to look at various independent variables to help control confounding; however, some confounders such as patient preference and pre-existing co-morbidities were unable to be assessed. All four neoadjuvant studies used large multicenter databases with large sample sizes ranging from 1556 to 354,204 participants. Since the likelihood is that the sample size in this proposed study will be much smaller than those used in the four neoadjuvant studies, it may be possible to reduce the risk of misclassification bias by crosschecking the data to ensure cases are properly identified as neoadjuvant or adjuvant therapy recipients for this proposed study. In addition, though no blinding will take place, the specialized training of the registrars at the NL cancer registry will help reduce the risk of information bias. Any additional data required will have to be with a chart review performed by the investigator. Therefore, increased diligence would be a necessity to prevent any mistakes made during

this data collection phase. If taken, these measures should help improve the rigor of this evaluation study.

Surgeons are the first contact that patients with breast cancer have in the oncology treatment realm. It is through a surgeons' referral that patients first access the services of medical and radiation oncologists. Evidence from all four neoadjuvant studies suggest that overall surgeons adhere to evidence-based clinical practice guidelines regarding neoadjuvant therapy referrals at a rate in the range of 44% to 79% for patients with stage III locally advanced disease, and 72% to 93% for patients with inflammatory breast cancer (Lin et al., 2017; Mohiuddin et al, 2016; Spronk et al., 2017). Graham et al. (2015) conducted a similar study in Alberta, Canada and found that 59% of those with locally advanced breast cancer received neoadjuvant treatment. Though this study did not meet the eligibility criteria for inclusion for this review due to its lack of an identifiable CPG, it was a Canadian study with results that confirms the range found in the four chosen neoadjuvant studies. There are few studies of this nature to predict accurately what an acceptable rate for guideline adherent neoadjuvant treatment should be for patients with locally advanced and inflammatory breast cancers. Though these ranges, especially at the lower end, for neoadjuvant therapy use reveal a poor uptake of a recommended standard of care, it seems a reasonable option to use them as target rates for guideline adherence for this project.

Adjuvant Therapy Studies

Findings. Five of the nine studies classified under the heading of adjuvant therapy in Table 3 of the appendix investigated the rates of receiving guideline-adherent treatment for breast cancer (Anderson et al., 2015; Campbell, Janitz, Vesely, Lloyd, & Pate, 2015;

Holleczek & Brenner, 2014; Verschoor et al., 2016; Wu et al., 2012). The two American studies found an overall range of guideline-concordant adjuvant care of approximately 90% to 92% (Anderson et al., 2015; Campbell, Janitz, Vesely, Lloyd, & Pate, 2015). In comparison, a third American study by Wu and colleagues (2012) indicated that 35% of patients did not receive guideline-adherent chemotherapy (only 65% did) and 20% of patients received inappropriate endocrine therapy (80% did) according to guideline recommendations. The authors suggested that the stark difference between their study results and studies performed by those such as Anderson et al. are probably due to the NCDB data being affiliated with accredited facilities (mentioned on page 7). In comparison, Wu et al. study data are from the cancer registries of several southern states, considered to be poorer with fewer available resources. Since all three of the studies were performed during the same time, there may be some merit to this argument by Wu et al. Meanwhile, Campbell and colleagues collected their data from one the cancer registry of only one state and though the data are from multiple centers within the state, it may restrict the data from being generalizable to other states. Lebeau et al. (2011) used odds ratios to determine the compliance with a CPG. These authors found that non-compliance to national guidelines was associated with older age (OR 2.1; 95% CI: 1.3 – 3.6) and region of residence (or 3.0; 95% CI: 1.2 – 7.4). These authors found that non-adherent clinical decision-making for specific aspects of treatment was usually associated specific tumor features. For example, non-compliance with radiation therapy was associated with disease involvement of the lymph nodes, or the presence of peritumoral vascular invasion (OR 1.5; 95% CI: 1.01 -2.3) while non-adherence to the overall treatment plan was associated with positive lymph nodes (OR 2.0; 95% CI: 1.2-3.3), grade III versus grade I

tumors (OR,2.9; 95% CI: 1.4-6.2) and the regional care facility of choice (OR 3.5; m95% CI: 1.7-7.1).

The authors of the remaining two studies, one German and one Dutch, stratified their results by specific guideline adherent treatment options (e.g., use of chemotherapy, endocrine therapy, targeted therapy, breast conserving surgery, sentinel node biopsy,) and found an increased use of these treatments over time (Holleczek & Brenner, 2014; Verschoor et al., 2016). Holleczek & Brenner (2014) found that the use of adjuvant chemotherapy increased from 60% to nearly 80% over the ten-year study period, while the use of endocrine therapy increased from 80% to approximately 93% and targeted therapy use increased from 1%-2% to approximately 48% in the same timeframe. These authors also found that the implementation of sentinel node biopsy (SNB) increased from approximately 1% at the beginning of the study to approximately 62% by the end of the study, with a corresponding decrease in the use of axillary lymph node dissection. Verschoor and colleagues (2016) also found significant changes in the use of endocrine therapy (23% to 56%) and chemotherapy (11% to 44%) over the study time period.

In addition, three German studies investigated survival outcomes for adherence and non-adherence to guideline recommendations of adjuvant therapy (Schwentner et al., 2013; Wockel et al., 2010; Wolters et al., 2015). Wolters and colleagues (2015) stratified the time interval of the study period and found that recurrence-free survival (RFS) and overall survival (OS) had improved significantly from the earlier time interval (TI1) to the later time interval (TI2) (RFS: p <0.001, hazard ratio (HR) = 0.57, 95% CI: 0.49-0.67) (OS: p < 0.001, HR = 0.76, 95% CI: 0.66- 0.87). The authors also noted that patients who received 100% guideline adherent treatment tended to have better outcomes than those

who received non-guideline adherent therapy. Wockel et al. (2010) found that patients with a prolonged RFS and OS were significantly associated with guideline adherent treatment ($p = 0.0001$) and that patients who experienced a greater number of guideline treatment violations were more likely to have lower OS ($p = 0.0001$). Schwentner and colleagues (2013) investigated the participation of patients in adjuvant clinical trials and found that participants had an increase in RFS over non-participants ($p = 0.006$) but differences in OS were not statistically significant. The authors also found no survival advantage when both participants and non-participants adhered to guideline recommendations. However, both RFS and OS were significantly worse for non-guideline adherent participants (RFS: $p < 0.001$; OS: $p < 0.001$) and non-guideline adherent non-participants (RFS: $p < 0.001$; OS: $p < 0.001$).

Quality and Insights. All the studies had large sample sizes with the exception of the study by Lebeau et al. (2011) which had the smallest sample size of 926 participants. All the studies were also given a medium rating for quality except for the study by Lebeau and colleagues which was given a low rating. This was due to a series of issues with the study: using hospital chart reviews only for data collection (higher risk of misclassification bias); requiring patient consent to examine patient information which resulted in only accruing 67% of the eligible population (23% rejected or gave no response to requested consent); compliance to guidelines was only 57% (multidisciplinary meetings not fully established at time of study); and creating three groups for guideline compliance which were difficult to define and deemed to not be an optimal model choice. These issues created threats to the internal validity of the study resulting in a low rating for quality. Therefore, only those studies awarded a medium rating for quality will

be considered in determining the measures or methodology for this practicum project. The issues noted with this study are all important pitfalls to avoid in conducting a quality study.

Advanced age was a common factor among the studies which affected whether patients received guideline-adherent treatment and likely will be the case for this proposed study. On average, those who were ≥ 75 years were at higher risk for non-guideline adherent treatment or guideline violations. All studies stratified the age of patients into intervals which is particularly beneficial for de-identification purposes. However, it is also helpful in isolating the age where many physicians become more cautious about exposing elderly patients to treatments capable of great harm, especially in the presence of frailty and pre-existing co-morbidities.

Breast Conserving Therapy

Findings. These grouped studies are in Table 4 of the appendix. White and colleagues (2010) investigated the use of guideline-recommended breast conservation surgery (BCS) for the surgical treatment of ductal carcinoma in situ (DCIS) before (2002-2003) and after (2006-2007) the introduction of a national Australian guideline. The authors found that the use of BCS did not change significantly over the study timespan (78% before versus 73% after); however, the utilization of SNB with BCS had increased from 2% pre-guideline implementation to 21% post-guideline implementation ($p < 0.001$). In addition, post-guideline implementation found that surgeons referred 67% of patients to radiation therapy (RT) compared to 58% pre-guideline implementation ($p = 0.04$). In a single hospital in the U.K., Mathew et al. (2017) found that 41% of women with DCIS had undergone SNB though only 14% had the recommended tumor-free margin width.

Patrick, Hasse, Feinglass, and Khan (2017) reported the BCS rate for women having stage I and II invasive breast cancer was 67%, between 1998 and 2011. On multivariate analysis of this American study, the authors determined that women who were younger (≤39 years), less educated, and living in rural areas were less likely to receive BCS. The utilization of post-BCS RT was on average 82% with a decrease in frequency of use for the youngest and oldest population. Persing and colleagues (2015) investigated the adherence of pathology reporting according to the College of American Pathologists guidelines and the impact on re-excision and mastectomy rates following BCS. These authors found that only 44% of cases were maximally compliant. In addition, the rates of re-excision or mastectomy after BCS were also statistically associated with non-compliant reporting.

Quality and Insights. This group of studies have mixed results in terms of usefulness in providing measures and methods information for this evaluation study. Mathew et al. (2017) was given a low rating for quality due to lack of generalizability and having an exceptionally long study period (1975 to 2008) where bias and/or confounding can occur from subtle changes over time. In addition, data being obtained from chart reviews at one hospital institution in the UK can introduce the concern of the potential lack of expertise of the data collectors in a hospital setting. Cancer registry data is collected by appropriately trained cancer registrars and without which the risk of misclassification bias is higher. The institution being studied is an academic–affiliated facility which one would expect to undergo progressive changes over the thirty-year period such as synoptic pathology reporting, change in computer systems or software which can contribute to improved margin measurement, and improvement in pathology slide fixatives and

protocols. These progressive changes can introduce a host of confounding factors which may affect the accuracy of margin reporting over time.

The remaining studies were awarded a medium quality rating. Patrick and colleagues (2017) had a very large sample size of 1,081,075 participants collected from the NCDB database while Persing et al. collected their sample of 1423 participants from the state of Vermont. Patrick et al. (2017) did find adherence to guidelines improved over time in terms of increasing rates of BCS, tumor-free margins, use of RT after BCS, and use of endocrine therapy and chemotherapy. Persing and colleagues (2015) also found advanced age (≥ 75 years) to be a significant indicator for withholding re-excision or mastectomy after BCS with positive margins.

White and colleagues (2010) had a smaller sample size of 342 participants and investigated the impact of a clinical practice guideline on the treatment of DCIS for a 12-month period prior to and after. Some of the demographic and tumor characteristics studied included stratified age intervals, detection method of tumor/disease, tumor size and grade, multi-focality, presence of necrosis, microcalcifications, and surgeon case-load. The guideline was broken down by specific recommendations and treatment and comparisons were made before and after the guideline was distributed, to determine effect. Bivariate followed by multivariate analysis captured the significant variables which affected the use of the new guideline. This study has a very similar methodology to what is envisioned for this proposed study, as well as the use of similar statistical measurement tools that should prove helpful in developing the evaluation plan.

Radiation Therapy

Findings. The four studies of this group are in Table 5 of the appendix. Two American studies explored the rates of post-mastectomy radiation therapy (PMRT) in different data sets and different study time spans. One of these studies by Berger et al. (2017) examined a large sample from a national cancer database of various accredited hospitals between 2006 and 2013. The results indicated that 62.3% of the study population received PMRT, with a highest proportion of these patients receiving guideline-compliant therapy in academic-affiliated centers. Dragun, Huang, Gupta, Crew, and Tucker (2012) conducted their study in Kentucky using the state tumor registry between 1995 and 2008 and found that only 47.3% of eligible patients received PMRT. The authors reported that women living in rural areas were less likely to undergo PMRT. The results of both studies also found that age (>70 years) and the lack of private insurance were associated with lower utilization of PMRT.

Struikmans et al. (2011) investigated the rates of guideline-adherent RT after breast conserving surgery (BCS) and found an increase in its use over time from 32%- 45% in 1997 to 41%-57% in 2008, though there were regional variations. On multivariate analysis, age $\geq$ 75 years and higher tumor stage were statistically significant factors associated with reduced use of RT after BCS. Regional variation was observed early in the study but adjusted to equivalency over time.

A study by Hattangadi, Taback, Neville, Harris and Punglia (2012) compared the rates of whole-breast irradiation (WBI) with that of accelerated partial breast irradiation using brachytherapy (APBIb) post-BCS between the years of 2000 and 2007. These authors found that only 2.6% of patients received APBIb and an astounding almost two-

thirds of those were deemed to be unsuitable or at the very least cautionary for this treatment regimen. Hattangadi et al. also found wide regional variability in APBIb use with the highest proportion being received in metropolitan areas.

Quality and Insights. These studies all received a medium rating for quality, had large sample sizes and are suitable for consideration for measures and methodology if warranted. The finding brought forth by Dragun et al. (2012) that patients living in rural areas tend to avail less often of certain treatment options, such as radiation therapy, when compared to those living in urban areas has been frequently encountered in our provincial cancer care program. Rural versus urban treatment choices are important factors to bear in mind when conducting this proposed study since one of the factors of interest being investigated is the differences between provincial hospital facilities and surgeons' referral rates for neoadjuvant treatment. Struikmans et al. (2011) also highlighted the issue of reduced guideline adherence for the elderly population.

Breast Cancer Treatment and the Elderly

Findings. Four studies were found on this topic and tabulated in Table 6 in the appendix. Three German studies explored the patterns of guideline-adherence and survival outcomes in the elderly diagnosed with breast cancer. Ebner and colleagues (2015) compared two groups according to age with one consisting of 50 to 69 years and the other consisted of those ≥ 70 years. Hancke et al. (2010) compared two similar age groups of women however these authors stratified the ≥ 70 years group into three additional groups (70 to 74, 75 to 79, and ≥80). In addition, van Ewijk and colleagues (2015) performed a comparison between a <65 age group with a 65-80 age group. All three studies found that the elder patients in each study were more likely to receive treatment with guideline

violations than their younger study counterparts [Ebner et al., 2015: 32.8% in 50-69 years versus 53.5% ≥ 70 years; Hancke et al., 2010: RT 9% for 50-69 years versus 33.7% for ≥ 70 years, chemotherapy (CT) 34.5% for 50-69 years versus 76.3% for ≥ 70 years; van Ewijk et al., 2015: 27% for < 65 years versus 42.7% for > 65 years for non-study participants]. The studies by Ebner et al. and van Ewijk et al. found that non-guideline adherent treatment was significantly associated with decreased disease-free survival (DFS), RFS and OS, though van Ewijk and colleagues found this to be true only when RT was omitted.

In 2004, an American study by McCormick and colleagues (2014) explored the guideline-concordant adjuvant treatment of women with hormone-receptor positive, stage I breast cancer who were ≥70 years of age. The recommendation at the time was to omit RT from the treatment regimen of these women after BCS. The results found that the pre-guideline implementation period only yielded a 17% omission of RT in this age group, while the post-guideline implementation period was not dramatically better with a 26% RT omission. Again, a wide variation was noted among NCCN institutions.

Quality and Insights. The studies in this group all received a medium rating for quality and all had relatively large sample sizes. The three German studies highlighted the strategy of stratifying the years of age to isolate the group where the most guideline violations occur. These studies have been helpful in determining the strategy for this study which will involve stratifying the patients ages in 10-year intervals, beginning with < 40 years, 41 to 50 years, 51 to 60 years, 61 to 70 years, and concluding with >70 years.

Molecular Profiling

Findings. Four studies looked at various aspects of molecular profiling of breast cancer and they are located in Table 7 of the appendix. A Dutch study by Schreuder et al. (2017) explored gene expression profiles (GEP) by utilizing the MammaPrint® 70-gene test for all women with hormone receptor positive BC who were stratified either has either low-risk or high-risk. This was not the indicated use for this test since it had initially gained approval for use for those women whose risk was moderate (neither clearly high- nor low-risk), and where the benefit of further treatment such as chemotherapy was unsure. The results found that 68.5% of patients were treated according to GEP result and not clinical presentation. GEP result alone was responsible for altering clinical low-risk patients to a high-risk category and vice versa, outside the recommendations of a national guideline.

Two German studies investigated the survival outcomes for triple negative breast cancer [estrogen receptor-/progesterone receptor-negative (ER/PR), human epidermal growth factor receptor 2-negative (HER2)] in women with invasive breast cancer. Schwentner et al. (2013) and Schwentner et al. (2012) found that 9.2% and 10.0% of the non-metastatic breast cancer population had triple-negative breast cancer, respectively. Both studies found that DFS/RFS and OS were significantly worse for those with triple-negative breast cancer compared to those with non-triple-negative breast cancers. In addition, both studies found that guideline violations were significantly more likely in the treatment of triple-negative breast cancers than non-triple-negative breast cancers ($p < 0.001$). An American study by Chen and Li (2015) explored breast cancer subtypes and investigated whether an association existed with race or ethnicity. The authors found that

American Indians and Alaskan native were four times as likely to be diagnosed with stage IV triple-negative breast cancer. In addition, African American women had a 40% to 70% higher risk of developing stage IV breast cancer and guideline violations were more likely to occur in the treatment of African American and Hispanic women.

Quality and Insights. All these studies received a medium rating for quality and varied from large to very large sample sizes. Though hormone receptor and HER2 receptor testing is usually performed on the definitive surgical specimen, surgeons or oncologists can request testing be performed on the biopsy specimen (providing enough tissue is available). The likelihood is that this information would not be available to the surgeon in the majority of cases when the time of decision-making is at hand. The initial plan for this proposed study had been to only collect information that would have been available to the surgeon at the time of decision regarding treatment sequencing. However, the two German studies influenced the decision to request the pre- or post-operative hormone receptor and HER2 receptor status on all patient cases from the cancer registry. This would aid in the attempt to identify the cases that would have benefited the most from neoadjuvant therapy such as the triple negative and HER2 positive cases. The study by Chen and Li (2015) is a very interesting one however, the provincial cancer registry does not collect race or ethnicity data on patients and therefore would not be a suitable independent variable to pursue.

Staging Investigations

Findings. Three studies, in Table 8 of the appendix, examined the rates of unnecessary staging investigations for women with early-stage breast cancer. The American study by Hahn et al. (2015) found that about 15% of patients had obtained at least one imaging test

and approximately half of those tests had been ordered for symptom investigation. The two remaining studies were Canadian, one by Han et al. (2012) which collecting their sample population from the patient records at a single hospital in Toronto, Ontario while the other, conducted by Simos et al. (2015), extracted their data from Ontario's tumor registry. Though the sample size was small (in relation to most of the 39 studies used), Han and colleagues found that at least 55% of their sample population had undergone unnecessary imaging tests for stages I, II, and III breast cancer. However, distant metastasis was found in only 1.3% of those investigated and all had stage III disease. Simos and colleagues had a much larger sample size (26,547) and found 85.9% of those patients had undergone at least one investigational imaging test, though the mean for each patient was 3.7 tests. Despite guidelines which recommended against routine imaging for stage I and II BC patients, 79.6% and 92.7%, respectively underwent inappropriate testing.

Quality and Insights. All three studies were given a medium rating for quality. The first two studies had large sample sizes while Han et al. was much lower at 231 participants. Though the results of the Han et al. (2012) study were from a single institution, the results are still generalizable if the sample population is similar to the target population of interest. The use of the cancer registry database for the proposed study will allow access to multiple centers around the province and have a similar sample population which should increase its generalizability as well. Both Canadian studies were conducted in Ontario and are likely more reflective of the pattern for inappropriate imaging for staging within other provinces. Non-adherence to breast cancer guidelines has been a problem in Canada for many years (Latosinsky, Fradette, Lix, Hildebrand, & Turner, 2007) and the

findings of the two Canadian studies in this group are a reminder that this may also be the case in this proposed study.

Tumor Characteristics

Findings. The two German studies in this group are in Table 9 of the appendix. They explored certain breast cancer characteristics such as the locality of tumors and bilateral versus unilateral tumors in order to determine whether the presence of either were associated with survival outcomes. In another study by Schwentner, Wolters, Wischnewsky, Kreienberg, and Wockel (2012), 4.3% of breast cancer cases were found to be bilateral while the remainder were unilateral only. The authors found that despite bilateral breast cancer having a poorer RFS and OS, fully guideline-concordant therapy was only obtained by 15.7% of all bilateral patients. In addition, as the number of guideline violations increased, the survival outcomes decreased. Wolters and colleagues (2015) found that unifocal tumors comprised 79.2% of the breast cancer cases included in the study while 15.6% had multifocal disease and 5.2% were diagnosed with multicentric disease. According to Zhou et al. (2013), whether tumors are multifocal or multicentric depends upon which anatomical quadrant of the breast the tumor resides. Multiple foci of tumor (multifocal) are located within the same quadrant while multicentric disease are in different quadrants of the breast. Wolters et al. (2015) found that the results of their study indicated that RFS was significantly worse for multifocal ($p = 0.007$) and multicentric ($p = 0.019$) disease compared to unifocal tumors, while OS was significantly inferior for multicentric ($p = 0.001$) disease but not for multifocal tumors ($p = 0.321$). In addition, guideline-concordant therapy was lower in the multifocal and multicentric disease in comparison to unifocal tumors ($p < 0.001$).

Quality and Insights. Both studies by Schwentner et al. (2012) and Wolters and colleagues (2015) received a medium rating for quality and had large sample sizes. The results of both studies have influenced the request for data related to the pre-surgical imaging detection of bilateral versus unilateral disease and the presence of multicentric, unifocal or multifocal disease.

Axillary Evaluation

Findings. Two studies, in Table 10 of the appendix, explored the surgical evaluation of the lymph nodes of the axilla in the treatment of invasive breast cancer and DCIS. Chong et al. (2013) investigated the use of axillary lymph node dissection (ALND) after SNB in women with early stage invasive breast cancer. These authors found that despite 24.1% of the sample population with ≤ 3 cm tumors having at least one positive sentinel node, only 78.7% of these went on to undergo an ALND. In addition, in the remaining 75.9% of the sample population with ≤ 3 cm tumors who had a negative sentinel node, 9.6% went on to undergo ALND. In tumors > 3 cm, half of the sample population had at least one positive sentinel node though 15.3% of these patients did not go on to have an ALND. In this same cohort, an ALND was performed on 21% of patients who had a negative sentinel node.

The second study was conducted by Mitchell et al. (2017) who investigated the patterns of surgical evaluation of the axilla in patients with DCIS. The authors reported that BCS was performed in 63% of the cases with the use of SNB increasing from 7.2% to 39.4% over the span of the study ($p < 0.01$). For patients who received a total mastectomy (37%), the use of SNB also increased over the study period from 24.3% to 77.1% ($p < 0.01$). Mitchell and colleagues also found that academic/research hospitals

were more likely to evaluate the axilla for both total mastectomy and BCS patients compared to that of community hospitals.

Quality and Insights. Both studies were rated medium for quality and had large sample sizes but neither offered any insights for the purposed study since the independent variable of interest would primarily be the clinical presentation of nodal involvement not the surgery that followed.

Single Studies

Findings. Van Bommel et al. (2017), a Dutch study in Table 11, found that younger patients (<50 years) with invasive breast cancer were more likely to undergo immediate breast reconstruction than older patients (50-65 years) while younger patients with multifocal disease underwent immediate breast reconstruction more frequently.

In an American study in Table 12, Stuckey et al. (2016) found that, in a sample of 314 patients eligible for genetic counselling and testing, only 34.1% were referred. Women who were more likely to be referred were those with a suspicious family history and those who chose a contralateral mastectomy.

In Table 13, a study by Grandjean et al (2012), with a small sample size of 196 patients, conducted an evaluation of the adherence to a 5-year follow-up guideline. The first year included fewer follow-up visits than recommended while the second to the fifth years indicated more visits than recommended took place. However, 28% of the sample were lost to follow-up before completing the full five years.

Quality and Insights. Van Bommel et al. (2017) had a large sample size while Stuckey et al. (2016) was smaller with 314 participants. Both studies received a medium rating for quality. However, Grandjean et al. (2012) received a low rating due to the loss of nearly a

third of their sample population which likely compromised the study findings. These studies provided little or no insight into the purposed study.

Guideline Adherent Studies Summary

Not all 39 studies were useful in providing insight into the modeling of this evaluation study in terms of its methodology and measurement features, though many of them were. The configuration of my study will closely resemble that of White et al. (2010) which will involve collecting data on all patients diagnosed with breast cancer who are eligible for neoadjuvant therapy for a 12-month period before and a 12-month period after the implementation of the Eastern Health BDSG neoadjuvant guideline. The proportion of patients who were referred for neoadjuvant treatment will be calculated for each of the two calendar years and compared to determine whether any significant change has occurred in the rate. Since most of the 39 studies used chi-square testing to determine differences in rates over time, this measurement will be used for this study as well. Important strategies have been underscored by reviewing these studies such as reducing the threats to the internal and external validity of the proposed study by:

- Having the services of a trained registrar to collect the data from the cancer registry to protect against selection, misclassification and information biases;
- Extensive oncology experience of the investigator will be beneficial in ensuring the accuracy of the neoadjuvant and non-neoadjuvant data from the chart review to control for misclassification bias;
- Investigating multiple independent variables in order to reduce, as much as possible, the effect of known confounders;

- Using appropriate statistical testing with a criterion for statistical significance (alpha = 0.05).

These strategies will be effective in producing a study plan that exhibits quality and rigor. Other insights and suggestions offered by these studies are:

- Identify cases with missing data (e.g., missing clinical AJCC staging) and exclude when a chart review does not recover the missing data. Document the number and reasons for exclusion in the final report;
- Stratify the patient age in intervals such as < 40, 41 to 50, 51 to 60, 61 to 70, > 70 years;
- Use the calculated ranges of neoadjuvant treatment for locally advanced and inflammatory breast cancers as a target rate of guideline adherence;
- Expect there will be some rural versus urban differences in neoadjuvant referral rates;
- Will not access patient-related information such as patient preference or pre-existing co-morbidities;
- The likelihood is that few older patients (>70 years) will be referred for neoadjuvant consideration.

Factors Which Influence Surgeons Decision

Study Findings

The 39 grouped studies did provide some insight into which patient characteristics, tumor-related, and facility-related data should be collected for this evaluation study. In addition, the research literature retrieved from the third literature search has also been

helpful in narrowing the list of potential independent variables that require data collection. A recent Canadian research study by Urquhart et al. (2016) used semi-structured interviews to explore the decision-making of surgeons related to utilizing a referral to oncology services for consideration of (neo)adjuvant treatment. The authors described seven factors which appear to influence a surgeons' decision-making through the clinical encounter, mediating factors, and the outer context. These are "…indications and contraindications for therapy; patients' beliefs and preferences; a belief that oncologists are the experts; knowledge of local standards of care; consultation with oncology colleagues; navigating patient logistics; and system resources and capacity" (Urquhart et al., 2016, E11). During the semi-structured interviews for this study, all of the surgeons felt that there was a lack of formal processes in place to enable them to consult with their oncology colleagues. In the absence of which, these surgeons believed informal discussions with their fellow surgeons aided in treatment decision-making and doing so would be sufficient to improve the quality of care.

Mamounas et al. (2016) used the answers of an online survey to evaluate how disease- and patient-related factors influenced the surgeon's decision to refer patients with breast cancer to medical oncology services, for a discussion regarding neoadjuvant therapy. These authors identified 11 of these disease- and patient-related factors which included:

- Skin/chest wall involvement;
- Tumor size;
- Histologic grade and type;

- HER2 status;
- Estrogen and progesterone status;
- Inflammatory breast cancer;
- Clinical assessment of axillary lymph node involvement;
- Patient's age;
- Patient's health and comorbidities;
- Patient's preference for timing of surgery; and
- Patient's level of interest in BCS (p.3511).

In addition, all four of the neoadjuvant studies investigated independent variables such as patient demographics, tumor features, facility type and location to determine whether any of these factors were associated with the utilization of neoadjuvant therapy (Killelea et al., 2015; Lin et al., 2017; Mohiuddin et al., 2016; Spronk et al., 2017). The findings of these studies for locally advanced disease suggest that younger age (<50 years) and larger clinical tumor size (T3, T4) are both positive indicators for receipt of neoadjuvant therapy, with a trend for increased use over time. Evidence in three of the studies also suggested a wide variation in neoadjuvant treatment utilization (i.e., referral to medical oncology) in relation to hospital type, with higher rates in academic healthcare facilities (those affiliated with a university) than those without this affiliation, such as community and cottage hospitals (Lin et al., 2017; Mohiuddin et al., 2016; Spronk et al., 2017). Data on independent variables, such as patient and physician preference, which play a role in the decision-making are not typically available in retrospective designs of this nature and will also be the case in the proposed study as well.

Quality and Insights

Mamounas et al. (2016) provided a comprehensive list of patient characteristics and tumor-related factors which may influence the decision-making process of the surgeon. Though the study design of descriptive exploratory is described as weak in PHAC's critical appraisal tool, the quality of this study was found to be strong. Therefore, its use is approved for developing the list of factors to be investigated in the proposed study. Many of the factors highlighted in the Mamounas and colleagues' study were also used in the four neoadjuvant studies described in the previous section (pages 10 – 14). The only other useful tumor-related factors were identified from the tumor characteristics group which were bilateral versus unilateral tumors and the presence of multicentric and/or unifocal/multifocal disease (page 26 – 27). These factors may play a role in the decision-making process, however a consultation with a general surgeon is necessary to determine if this is so.

Though the initial plan was to only collect data available to the surgeon at the time of decision-making, it seems prudent to also collect data on tumor molecular subtyping in terms of hormone receptor status (i.e., ER/PR) and HER2 status. This information may be helpful at a later stage in promoting the use of neoadjuvant therapy especially for triple negative and HER2 positive tumors. The list of independent variables will be finalized after a consultation with a general surgeon. Many of the studies used multivariable analysis with the aid of a logistic regression model in order to determine what patient-, tumor-, and facility-related factors have a significant association with surgeons' treatment decision-making. This will also be the measurement strategy of choice for this evaluation study.

Conclusion

This literature review and summarization have been fundamentally important in developing a plan with which to evaluate whether clinical practice adheres to the recommended guidelines developed by the participants of the Eastern Health BDSG. It has provided an opportunity to examine the means necessary to protect and strengthen the internal validity of the proposed study, by reducing biases and confounding where possible. The knowledge gained will be instrumental in developing a study that reflects quality and rigor in its methodology. Performing a review of the work that has been completed by others can also help expedite and narrow the focus for this project. Combining this work with the knowledge gained from consulting with various institutional experts, identified in the practicum proposal will enable the conception of a comprehensive plan to gather the necessary data, perform the appropriate analysis, and determine whether the healthcare systems' referral process operates as intended for the benefit of our breast cancer population. If indicated, recommendations and system changes may be warranted to improve the quality of care delivered.

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Appendix

Table 1: Glossary of Abbreviations for Research Literature Summary

Abbreviation/ symbol	Definition	Abbreviation/ symbol	Definition
AHS	Alberta Health Services	DFS	Disease-free survival
ALND	Axillary lymph node dissection	ER- or ER neg.	Estrogen receptor-negative
ASCO	American Society of Clinical Oncology	ER+ or ER pos.	Estrogen receptor-positive
assoc.	Associated	ET	Endocrine therapy
ASTRO	American Society of Radiation Oncology	f/u	Follow-up
BCS	Breast conservation surgery	HER2 – or HER2 neg.	Human epidermal growth factor receptor-negative
BCT	Breast conservation therapy	HER2 + or HER2 pos.	Human epidermal growth factor receptor-positive
BL	Borderline lumpectomy candidates	HR	Hazard ratio
b/w	Between	Hx	History
CI	Confidence interval	LA	Locally advanced
CCO	Cancer Care Ontario	LCIS	Lobular carcinoma in situ
CPG	Clinical practice guideline	LN	Lymph nodes
CT	Chemotherapy	LR	Local recurrence
DCIS	Ductal carcinoma in situ	MRI	Magnetic resonance imaging

Abbreviation/ symbol	Definition	Abbreviation/ symbol	Definition
LVI	Lymphatic vascular invasion	RFS	Recurrence-free survival
NAC	Neoadjuvant chemotherapy	RR	Relative risk
NCCN	National Comprehensive Cancer Network	pt.	Patient
NICE	National Institute for Clinical Excellence	RT	Radiation therapy
NST	Neoadjuvant systemic therapy	SN	Sentinel node
OR	Odds ratio	SNB	Sentinel node biopsy
OS	Overall survival	SOC	Standard of care
PMRT	Post-mastectomy radiation therapy	TNBC	Triple negative breast cancer (means ER-, PR-, & HER2-)
PR- or PR neg.	Progesterone receptor-negative	TT	Tri-modality therapy (means surgery, chemotherapy & radiation therapy)
PR+ or PR pos.	Progesterone receptor-positive	vs.	Versus
PS	Performance status	yrs.	Years

Research Literature Summary Tables

Table 2: Neoadjuvant Therapy for Locally Advanced/Inflammatory Breast Cancer

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
1. Killelea et al., (2015). USA Retrospective cohort design Objective: To analyze national trends in breast conservation therapy (BCT) after neoadjuvant chemotherapy (NAC).	• N = 354,204; • Convenience sample from a national cancer database b/w 2006 and 2011; • Inclusion criteria - women with stage I to III invasive BC; • Exclusion criteria – clinical stage T4; • NCCN guideline: Recommends pts with stage IIA, IIB, and certain stage IIIA, if BCS is desired, should be offered NAC. • Primary endpoint: Rates and patterns of BCT and NAC treatment in BC.	• Overall, 169,376 (47.8%) underwent lumpectomy, with decreasing rates of 51.3% in 2006 to 46.5% in 2011; • Overall, 59,063 (16.7%) received NAC, with rates increasing significantly from 13.9% in 2006 to 20.5% in 2011 ($p < 0.001$); • For tumors > 3 cm, NAC consistently led to an increased rate of BCT (70% increase in odds of BCT with NAC compared to adjuvant therapy) (OR 1.7; 95% CI: 1.6, 1.8); • Pathological complete response rate was 29.7% in this cohort (7880 pts) with lumpectomy rate of 41% for this group.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Direct Evidence <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing data on use of NAC for pts in pursuit of BCT but ultimately had a mastectomy due to presence of positive margins which may introduce selection bias; • Does not account for patient-related confounding factors such as treatment preference.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
2. Lin et al., (2017). USA Retrospective cohort design Objective: To compare facility-level and patient-level factors in the use of trimodality therapy (TT) of CT, RT and surgery for the treatment of nonmetastatic inflammatory BC.	• N = 5537; • Convenience sample from a national cancer data base b/w the years of 2003 to 2011; • Inclusion criteria – women with non-metastatic inflammatory BC who underwent locoregional treatment; • Exclusion criteria – those who didn't eventually undergo surgery, had a prior cancer dx., and those treated at a healthcare facility which had treated <5 pts with inflammatory BC over study period; • NCCN guideline: The treatment of non-metastatic inflammatory BC should include TT. • Primary endpoints: Rates of TT in non-metastatic inflammatory BC.	• Use of TT fluctuated annually over study period (range, 67.3% - 75.7%); • On multivariate model, use of TT more likely among the young, higher income, pathologic N1 tumors (all *p* <.05); • Use of TT was not found to be statistically significantly associated with type of facility (*p* = .33); • The variance attributable to facility-level factors was substantial at 11% while the variance attributed to pt.-level factors was 3.4% for the underuse of TT.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Direct Evidence <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • May have missed cases assigned to non-regular physician providers creating selection bias; • Difficulties encountered in drawing conclusions about improvement in pt care because of limited outcome variables available from the database used; • This database only collected two facility-level factors, without physician-level data which may create confounding.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
3. Mohiuddin et al., (2016). USA Retrospective cohort design Objective: To examine the patterns of neoadjuvant chemotherapy (NAC) and neoadjuvant ET use among younger women in various cancer centers.	• N = 118,086; • Convenience sample from a national cancer data base, b/w 2006 and 2012; • Inclusion criteria - women < 65 yrs with clinical stage IIA (T2N0 only) to IIIC BC (stratified into two groups: locally advanced (LA) and borderline eligible for lumpectomy (BL); • Exclusion criteria – those with earlier breast cancers, metastatic disease, incomplete data on stage/receipt of systemic therapy/primary surgery; • NCCN guideline: Recommend neoadjuvant systemic therapy for pts with LA and BL candidates who desire BCS. • Primary endpoint: Neoadjuvant systemic therapy rates in those < 65 with BC.	• The LA group included 20,720 pts (including an inflammatory BC group of 3591); • Use of NAC (± ET) in LA group was especially high for T4 disease (79% for stage IIIB non-inflammatory BC and 93% for inflammatory BC); • Across almost all stages and receptor subtypes, the use of NAC was lower in community vs academic centers; • Multivariate analysis revealed use of NAC in community was lower than academic centers (BL candidates: adjusted risk ratio (RR) 0.73; 95% CI: 0.69, 0.77) (LA candidates: adjusted RR 0.78; 95% CI: 0.74, 0.83); • Overall use of neoadjuvant ET alone was rare (⩽ 2%) for all stages.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Direct Evidence <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing data on use of NAC may introduce selection bias; • Does not account for patient-related confounding factors such as treatment preference.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
4. Spronk et al., (2017). Netherlands Retrospective cohort design Objective: To examine the clinical practice of neoadjuvant chemotherapy (NAC) for stage III BC pts in all Dutch hospitals.	• N = 1556; • Convenience sample from a national BC audit database, from 2011 to 2015; • Inclusion criteria – women aged 18-70 yrs with stage III BC, treated surgically; • Exclusion criteria - ≥70 yrs., a prior cancer diagnosis, unknown sequence of chemo and surgery; • National Dutch BC guideline recommends NAC for pts with stage III BC aged <70 yrs. • Primary endpoint: Rates of NAC in stage III BC.	• A total of 1230 of the 1556 pts (79%) received NAC; • No change noted in use of NAC over time, but a large variation in use of NAC was noted b/w hospitals (0 - 100%); • Significant independent predictors of NAC were age <50 yrs, breast MRI, large tumor size, advanced nodal disease, hormone receptor negative status and hospital participation in neoadjuvant clinical trials (all $p < 0.001$); • NAC use in stage III BC was not influenced by hospital type and hospital surgical volume.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Direct Evidence <u>Strengths</u> • Large sample size; • Multicenter study of all Dutch hospitals included (100% enrollment). <u>Limitations</u> • Potential for misclassification bias or coding errors; • Does not account for pt-related factors such as preference or lack of knowledge concerning NAC option, which may create confounding.

Table 3: Adjuvant Therapy

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
5. Anderson, Morris, Kimmick, Trentham-Dietz, Camacho, Cheng, …& Lipscomb. (2015). USA Retrospective cohort design Objective: To examine local definitive treatment for non-metastatic BC.	• N = 6505; • Convenience sample from a pooled data of 7 state or regional cancer registries in 2004; • Inclusion criteria - women with stage 0 to IIIA primary BC; • Exclusion criteria – those with locally advanced or metastatic disease; • NCCN guideline: Recommends local definitive therapy as indicated with primary surgery, node dissection, and use of RT based on stage of disease. • Primary endpoints: Rates of guideline concordant loco-regional treatment for BC.	• Approximately 90% received guideline concordant loco-regional treatment (GCLRT); • The odds of BCS vs mastectomy were higher for increased yrs of age (OR= 1.01, p = 0.031), higher tumor stage (OR= 0.49 and 0.21, p = 0.002 for stage II and IIIA respectively) public insurance, and presence of mild comorbidity; • RT following BCS was the most omitted treatment component causing non-concordance in the study population (only 80% received RT); • In multivariate regression, effects of treatment facility, DCIS, race, and comorbidity on non-concordant care differed by age.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias due to missing data and use of data from accredited cancer programs; • Data does not account for influence of pt choice which can introduce confounding; • Data did not reflect sentinel lymph nodal assessments during that year which may introduce confounding.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
6. Campbell, Janitz, Vesely, Lloyd, & Pate. (2015). USA Retrospective cohort design Objective: To describe the extent to which pts receive guideline-based, stage-specific treatments for localized invasive BC.	• N = 4177; • Convenience sample from a single state-wide cancer registry b/w 2003 to 2006; • Inclusion criteria – women with localized or early-stage BC; • Exclusion criteria – those with metastatic disease, identified through death certificate or at autopsy, Hx of cancer, diagnosis by mammogram without pathological confirmation, out-of-state cases, mesotheliomas, Kaposi sarcomas, and lymphomas; • NCCN guideline: Recommends primary treatment total or modified radical mastectomy or BCS followed by RT ± CT and/or ET for localized or early-stage BC as SOC (standard of care). • Primary endpoints: Rates of guideline-directed SOC in BCS pts.	• Overall, 92% of cohort were treated with recognized SOC; • However, in ⩾65 yrs group, the only variables related to SOC were age, primary payer, and comorbid conditions; • Women ⩾75 yrs had a lower odds of meeting SOC than those 65-74 yrs (OR 0.30; 95% CI: 0.20, 0.43); • Those ⩾65 yrs without insurance, with comorbidities, or with unknown comorbidity status had significantly lower odds of meeting SOC; • Among those < 65 yrs of age, insurance type, diagnosis year, larger tumor size, and comorbidities were associated with meeting SOC.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing data on comorbidities can introduce selection bias; • Lack of information on ER, PR, and HER2 status could introduce potential confounding related to the effect it would have on treatment options; • Lack of individual data on poverty or education which could introduce confounding and limit study strength; • Data from only one state and therefore may not be generalizable to other state(s).

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
7. Holleczek & Brenner. (2014). Germany Retrospective cohort design Objective: To examine the usage of BC treatment, the extent of adherence to CPG, and survival of BC pts according to recommended treatment options.	• N = 8571; • Convenience sample from a state-wide cancer registry b/w 2000 and 2009; • Inclusion criteria – women ≥15 yrs with invasive BC; • Exclusion criteria – previous history of BC, in situ disease; • German national guideline (S3): Recommends specific treatment decisions based on tumor-related factors. • Primary endpoints: Rate of guideline-adherent treatment usage, relative survival, relative excess risk (RER) in BC.	• Increasing guideline adherence seen over time; • Use of BCS increased from 59% to 67% over time span of study; • Rise in use of SNB (62%) over time; • CT use for lymph node pos. or hormone receptor neg. tumors increased from 60% to 79%. Use of ET for hormone receptor pos. or mixed tumors rose from 79% to 93%, while trastuzumab treatment use for HER2 positive tumors rose to 47%; • Non-guideline compliant treatment was associated with increased cancer-related mortality [e.g., LN+ /HR-ve BC not treated with CT had a 5-yr relative survival of 29% (Relative Excess Risk of death (RER): 2.89, 95% CI: 1.46, 5.71) compared to 54% for pts who received CT].	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing comorbidity data may create selection bias; • Data from one state may not be generalizable to rest of the country; • Confounding factors may affect outcomes.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
8. Lebeau, Mathoulin-Pelissier, Bellera, Tunon-de-Lara, Daban, Lipinski, …& Migeot. (2011). France Retrospective cohort design Objective: To measure the compliance with CPGs for the management of non-metastatic BC care and to identify factors assoc. with non-compliance at a clinical and organizational level.	• N = 926; • Convenience sample from pt. medical records from multiple centers b/w 2003 and 2004; • Inclusion criteria – women with invasive unilateral BC; • Exclusion criteria – metastatic disease, previous cancer diagnosis; • French national guideline: Recommends treatment for non-metastatic according to pt. and tumor characteristics. • Primary endpoint: OR	• Non-compliance with clinical decisions for treatment was assoc. with older pt. age (OR 2.1; 95% CI: 1.3, 3.6) and healthcare region (OR 3.0; 95% CI: 1.2, 7.4); • Non-compliance with clinical decisions for RT was assoc. with LN involvement or the presence of peritumoral vascular invasion (OR 1.5; 95% CI: 1.01, 2.3) and non-compliance with overall treatment was assoc. with presence of positive LNs (OR 2.0; 95% CI: 1.2, 3.3), grade III vs grade I (OR 2.9; 95% CI: 1.4, 6.2), and one healthcare region vs another (OR 3.5; 95% CI: 1.7, 7.1).	Strength of Study Design: Moderate Quality of the Study: Low Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size; • Multicenter study. <u>Limitations</u> • Much higher potential for misclassification bias or coding errors due to data collected from medical records; • Having to obtain patient consent allowed for a loss of 23% of the eligible population which probably introduced selection bias; • Missing data created selection bias in an inability to explain non-compliance; • Potential for confounding.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
9. Schwentner, van Ewijk, Kurzeder, Hoffman, Konig, Kreienberg, …& Wockel. (2013). Germany Retrospective cohort design Objective: To determine whether BC participation in adjuvant clinical trials improves survival, and whether guideline adherent adjuvant therapy is an equal alternative.	• N = 9433; • Convenience sample from a specialized multi-center BC database b/w 1992 and 2008; • Inclusion criteria – women with BC (either in a clinical trial or not) who received adjuvant therapy; • Exclusion criteria – in situ disease, metastatic disease, bilateral BC, occult disease, phylloides, and those with incomplete f/u, and unknown study participation status; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS in BC.	• 13.3% (1255) participated in adjuvant clinical trials (PA) while 86.7% (8178) did not (NPA); • RFS higher among PA than NPA ($p = 0.006$) but no significant difference in OS; • No significant difference b/w guideline adherent NPA compared to PA; • However, survival was significantly poorer in both non-guideline adherent PA (RFS: $p < 0.001$) (OS: $p < 0.001$) and non-guideline adherent NPA (RFS: $p < 0.001$) (OS: $p < 0.001$) as compared to guideline adherent PA.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Selection bias in clinical trial eligibility criteria; • Confounders can affect treatment/outcomes, especially co-morbidities.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
10. Verschoor, Kuijer, Verloop, van Gils, Sonke, Jager, …& Elias. (2016). Netherlands Retrospective cohort design Objective: To assess the impact of treatment guideline changes on the administration of adjuvant systemic therapy (AST) in early-stage BC pts and the adherence of such on a nation-wide level.	• N = 124,472; • Convenience sample from a national cancer registry, b/w 1990 and 2012; • Inclusion criteria – women with early-stage grade I – II BC who received AST; • Exclusion criteria – LA, or metastatic disease; • National Dutch guidelines: Recommends treatment for early-stage BC as per guideline at each given time period. • Primary endpoints: Rates of AST and guideline adherence in stage I and II BC.	• Adjuvant ET use increased from 23% to 56% over timeframe, while CT from 11% to 44%; • 8% received ET and 3% received CT without guideline indication, while 10% - 29% did not receive either ET or CT despite a guideline indication; • Unfavorable clinicopathological factors generally decreased the risk of under-treatment and increased the risk of overtreatment; • There was an increased risk of ET under-treatment in younger women (RR < 35 yrs vs 60-69 yrs 1.79; 95% CI: 1.30, 2.47) and in women with HER2+ disease (RR 1.64; 95% CI: 1.46, 1.85).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Does not account for confounding from lack of pt-related information such as adherence to therapy or specific reasons for nonadherence; • Selection bias may be present.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
11. Wockel, Kurzeder, Geyer, Novasphenny, Wolters, Wischnewsky, …& Varga. (2010). Germany Retrospective cohort design Objective: To analyze the impact of a German breast cancer guideline adherence on clinical outcomes.	• N = 3976; • Convenience sample from a specialized multi-center BC database b/w 2001 and 2005; • Inclusion criteria - pts with invasive BC; • Exclusion criteria – metastatic disease, in situ disease, bilateral tumors, occult carcinomas, phylloides or sarcomas, or if incomplete tumor excision occurred after surgery; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoint: RFS, OS.	• A significant assoc. exists b/w treatment adherence and prolonged RFS and OS (p = 0.0001); • The greater the number of violations in guideline adherence, the lower the OS (p = 0.0001); • Advanced age at diagnosis was assoc. with reduction in guideline adherence; • Guideline adherence for therapeutic modalities BCT, mastectomy, ALND, and ET was > 80%, CT guideline adherence was 71.4%.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Selection bias may have occurred due to risk assessment dataset excluding those > 70 yrs.; • Confounding factors such as physician-related barriers and pt.-related factors may have affected results.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
12. Wolters, Wischhusen, Stuber, Weiss, Krockberger, Bartmann, …& Diessner. (2015). Germany Retrospective cohort design; Objective: To determine whether clinical outcomes of women with BC have improved during the last 20 yrs irrespective of whether they were treated in accordance with clinical guidelines or not	• N = 9061; • Convenience sample from a BC specialized multicenter database b/w 1991 and 2009 [1991-2000 (TI1) & 2001-2009 (TI2)]; • Inclusion criteria - women with invasive BC and RFS $\geqslant$ 3 months; • Exclusion criteria – non-invasive BC, males, RFS < 3 months; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS.	• Clinical outcome of all pts significantly improved in TI2 compared to TI1 [RFS: $p < 0.001$, HR = 0.57, 95% CI (0.49, 0.67); OS: $p < 0.001$, HR = 0.76, 95% CI (0.66, 0.87)]; • OS and RFS of guideline-adherent pts also improved in TI2 compared to TI1; • The percentage of guideline-conforming systemic therapy (ET & CT) significantly increased ($p < 0.001$) in the time cohort TI1 - TI2 for the non-adherent group.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing comorbidity data may create selection bias; • Confounding factors may affect outcomes.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
13. Wu, Lund, Kimmick, Richardson, Sabatino, Chen, …& Lipscomb. (2012). USA Retrospective cohort design Objective: To explore how factors such as race/ethnicity, insurance, poverty and education, and facility were assoc. with the receipt of guideline-concordant adjuvant systemic therapy.	• N = 6734; • Convenience sample from a national program of seven state cancer registries from 2004; • Inclusion criteria – women ⩾20 yrs with invasive BC; • Exclusion criteria – previous history of cancer, Paget's disease, mesothelioma, Kaposi's sarcoma, lymphoma, in situ disease, diagnosis by autopsy or death certificate; • NCCN guideline: Recommends CT dependent upon specific tumor factors such as size, grade, histology, and LN status. • Primary endpoints: Rates of guideline-concordant receipt of adjuvant CT, regimens among adjuvant CT recipients, and ET.	• Overall, 35% of women did not receive guideline-concordant CT, 12% received non-guideline-concordant regimens, and 20% received non-guideline-concordant ET; • Significant predictors for receipt of non-guideline-concordant CT included age ≥ 65 yrs of age, race, insurance type, residing in high-poverty low-education areas, and treatment at non-specialized facilities; • Predictors of non-guideline regimen use included lack of insurance, poverty, and low education after adjustment; • Poverty and treatment at non-specialized facilities predicted non-guideline ET after adjustment.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study which allows generalizability. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Lost almost 20% of eligible cases due to missing data/information which may introduce selection bias; • One diagnosis year analysis does not allow for trend of change over time.

Table 4: Breast Conservation Therapy

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
14. Mathew, Karia, Morgan, Lee, Ellis, Robertson, & Bello. (2017). Great Britain Retrospective cohort design Objective: To assess predictors for local recurrence (LR) in pts undergoing breast conserving surgery (BCS) for ductal carcinoma in situ (DCIS).	• N = 582; • Convenience sample from a single institutions' databases and pt medical records b/w 1975 and 2008; • Inclusion criteria – women with DCIS who underwent surgical treatment (mastectomy and BCS) ±RT; • Exclusion criteria: previous history of treated invasive BC and developed subsequent DCIS; • Local guideline (prior to change in 2008): Margin width of ⩾10mm is preferred for pts undergoing BCS for DCIS. • Primary endpoint: Rates of DCIS LR in BCS.	• Overall, 239 women had BCS for DCIS, with overall LR rate of 17% (40/239); • LR more common in pts ⩽ 50 yrs (32%) vs > 50 yrs (14%) (p = 0.02); • LR for margins of <5mm was 43% vs 5-9mm with 12% vs ⩾10mm with 14% p = 0.01); • Multivariate analysis found age ⩽50 yrs, and <5mm pathological margins were independent prognostic factors for LR.	Strength of Study Design: Moderate Quality of the Study: Low Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size. <u>Limitations</u> • Potential for misclassification bias or coding errors. Though risk may be higher for misclassification error when data collected from individual hospital records; • Risk may also be higher for selection bias; • Data from single institution may not be as generalizable as multicenter studies; • Retrospective oncology data that covers a thirty-year period is open any number of confounding factors in terms of changes in treatment.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
15. Patrick, Hasse, Feinglass, & Khan. (2017). USA Retrospective cohort design Objective: To assess the progress in recent years of breast conserving therapy use in contemporary BC care.	• N = 1,081,075; • Convenience sample from a national cancer data base, b/w 1998-2011; • Inclusion criteria - women with invasive BC whose tumors were ⩽2 cm; • Exclusion criteria – those with missing stage at diagnosis, males, missing zip codes, missing margin info, missing RT status; • NCCN guideline: For stage I – II BCs with T1 tumors, BCS is recommended. • Primary endpoints: Rates of BCS and mastectomy in stage I and II BC.	• Overall, 67% received BCS and 33% underwent mastectomy; • Younger women (≤39 yrs) had the lowest odds of BCS (OR 0.49; 95% CI: 0.48, 0.50); • Rates of BCS were significantly lower by race, income, insurance type and education; • 95% of BCS pts had tumor-free margins, with younger women (≤39 yrs) being 28% (OR 0.72; 95% CI: 0.68, 0.76) less likely to have tumor free margins compared to women aged 50-69; • Overall,82% had post-lumpectomy RT and improved over time (less frequent in youngest and oldest); • Post-surgery ET use increased over time, while adjuvant CT use remained stable. ET use was significantly lower for race and education, while CT rates were lower as age increased.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias due to data collected from accredited cancer facilities only; • Does not account for patient-related treatment preference and co-morbidities which could introduce confounding.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
16. Persing, Jerome, James, Callas, Mace, Sowden, …& Sprague. (2015). USA Retrospective cohort design Objective: To determine whether compliance with the College of American Pathologists (CAP) guidelines affects re-excision and mastectomy rates after BCS with negative margins.	• N = 1423; • Convenience sample from a state-wide BC imaging service b/w 1998 and 2006; • Inclusion criteria – women whose initial BC surgery was BCS; • Exclusion criteria – all reports with 1 or more positive margins, path. reported from slide reviews, synchronous primaries, reports of no residual tumor found on excision following a positive biopsy; • CAP guideline: Recommends pathologists document distance to closest negative margin with further recommendation to include margin distance at all six specimen orientations. • Primary endpoints: Re-excision and mastectomy rates and the CAP compliance in BC.	• Pts with non-compliant margin reporting were 1.7 times (95% CI: 1.15, 2.48) more likely to undergo re-excision and/or mastectomy than those with maximally compliant reporting; • Level of compliance most strongly assoc. with frequency of mastectomy, with non-compliant margin reporting assoc. with a 2.5-fold increase (95% CI: 1.6, 3.8) in mastectomy rates compared to maximally compliant reporting; • Trend less clear for frequency of re-excision alone, although pts with minimal compliant reporting were more likely to undergo re-excision compared to pts with maximally compliant reports (OR=1.6; 95% CI: 1.1, 2.4).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Lack of data concerning additional decision-making factors that influence treatment options may have introduced selection bias; • Certain pathological features not reported may have influenced decision to re-excise therefore introducing confounding; • Other system-level factors may also affect re-excision and mastectomy rates which create confounding.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
17. White, Pruden, Kitchen, Villanueva, & Erbas. (2010). Australia Retrospective cohort design Objective: To examine the impact of the Australian treatment recommendations for DCIS on clinical practice and surgeons' attitudes to the recommendations.	• N1 = 342; • Convenience sample from a state-wide cancer registry b/w 2002/2003 and 2006/2007; • Inclusion criteria – women with DCIS before and after implementation of the guideline recommendations; • Exclusion criteria – LCIS, microinvasion; • Australian treatment guideline: Recommends image-guided core biopsy, obtaining clear margins, no ALND, RT after BCS. • Primary endpoint: Rates of cases adhering to guideline.	• Compared to pre-guideline implementation period, more BCS cases were referred to a RT oncologist (67% vs 58%) and more received RT (53% vs 44%) post-guideline implementation; • Tumors > 20mm, intermediate grade and moderate necrosis were more likely to receive RT post-guideline implementation; • Among BCS, an increase SNB use was noted over the study period, with SNB more likely for larger tumors and tumors detected outside the screening program (both $p < 0.01$); • Among mastectomy cases post-guideline implementation, the only factor assoc. with SNB was annual caseload ($p < 0.01$), with Drs. Treating 10-15 cases of DCIS more likely to perform SNB than those treating < 5 cases (OR 8.91; 95% CI: 2.25, 35.34).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias; • Does not account for confounding factors in RT use such as patient treatment preference.

Table 5: Radiation Therapy

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
18. Berger, Wang, Kaufman, Williamson, Ibarra, Pollitt, …& Yao. (2017). USA Retrospective cohort design Objective: To examine the compliance rates of a post mastectomy radiation therapy (PMRT) before and after an implemented 2008 quality measure (NAPBC) for BC patients with positive axillary lymph nodes (LN).	• N = 34,752; • Convenience sample from a national cancer data base b/w the years of 2006 to 2013; • Inclusion criteria – post-mastectomy women > 18 yrs with invasive BC with ⩾4 positive LN; • Exclusion criteria – multiple primary cancers, in situ or stage IV disease, or those who had neoadjuvant therapy; • NCCN/ASCO guidelines: Post-mastectomy pts with ⩾4 positive LNs should receive PMRT. • Primary endpoints: Rates of post-mastectomy RT.	• 62.3% or 21,638 of the sample received PMRT; • Significantly higher proportion of pts were treated with PMRT at accredited academic centers compared to non-accredited hospitals respectively (28% vs 16.4%); • Accredited academic centers also demonstrated considerably higher post-guideline compliance rates with PMRT than hospitals (2009: OR 1.41; 95% CI: 1.04, 1.93; 2011: OR 1.20; 95% CI: 1.00, 1.56); • Pts less likely to receive PMRT were older, had lower income, and had either Medicare/Medicaid or were uninsured.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • May have missed cases assigned to non-regular physician providers creating selection bias; • Difficulties encountered in drawing conclusions about improvement in pt care because of limited outcome variables available from the database used.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
19. Dragun, Huang, Gupta, Crew, & Tucker. (2012). USA Retrospective cohort design Objective: To analyze trends of PMRT for LA BC prior to and since the ASCO guidelines, as well as the disparities and barriers to recommended care.	• N = 8889; • Convenience sample from a state cancer registry b/w 1995 and 2008; • Inclusion criteria – women ⩾20 yrs with stage II (Group 1- T2, N0) (Group 2 – T1-2, N1) or III (Group 3 – T3-4, N2-3) BC; • Exclusion criteria – in situ disease, stage I or IV disease, previous history of cancer, first course treatment other than mastectomy; • ASCO guideline: Recommends PMRT is SOC for most stage II and III BC. • Primary endpoints: Rates of PMRT over time.	• 24% received PMRT over study period (rates for Groups 1, 2, and 3 were 7.5%, 19.5%, and 47.3%, respectively); • Since 2001, use of PMRT increased from 21.1% to 26.5%, p <0.0001, occurring mainly in Group 3 (from 40.8% to 51.2%, p <0.0001); • The average rate of PMRT remained constant in Group 1 and decreased in Group 2; • Rate of PMRT was significantly lower in those >70 yrs, diagnosis prior to 2001, rural populations, and Medicare pts (all p < 0.0001); • In terms of disease specifics, pts was less likely to receive PMRT if they had stage II cancer, smaller tumor size, limited axillary surgery, or well-differentiated and/or ductal histology (all p < 0.0001).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for missed data makes selection bias a fundamental risk with non-randomized data; • Potential for confounding factors.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
20. Hattangadi, Taback, Neville, Harris, & Punglia. (2012). USA Retrospective cohort design Objective: To evaluate patterns of accelerated partial breast irradiation using brachytherapy (APBIb) use after BCS compared with external beam whole breast irradiation (WBI) and whether APBIb treatment was concordant with guidelines.	• N = 138,815; • Convenience sample from a national multi-center database of tumor registries b/w 2000 and 2007; • Inclusion criteria – women with DCIS or invasive BC; • Exclusion criteria – previous cancer diagnosis, diagnosis obtained through death certificate or autopsy; metastatic disease, LCIS, mastectomy, incomplete RT information; • ASTRO guideline: Recommends appropriate pt. selection for APBI application based on pt. characteristics and clinical factors (3 groups – suitable, cautionary, & unsuitable. • Primary endpoints: Rates of WBI and APBI, and rates of guideline adherence.	• Overall, 2.6% (3576) of pts received APBIb, and 65.8% of them were classified as cautionary or unsuitable; • 5% of pts who received APBIb were deemed suitable, 3.4% were deemed cautionary, and 1.6% were deemed unsuitable by guideline standards ($p < 0.001$); • APBIb use increased from 0.4% in 2000 to 6.6% in 2007 and vary widely b/w regions and institutions; • For pts with invasive BC, black women (OR 0.80; 95% CI: 0.70, 0.92; p=0.002), Hispanic women (OR 0.78; 95% CI: 0.67, 0.90; p<0.001), and "other" races (OR 0.5; 95% CI: 0.41, 0.62, p <0.001) were less likely to receive APBIb than white and non-Hispanics women.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for missing data and a resulting selection bias; • No discussion on study limitations; • Potential for confounding factors.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
21. Struikmans, Aarts, Jobsen, Koning, Merkus, Lybeert, …& Coebergh. (2011). Netherlands Retrospective cohort design Objective: To evaluate the use of primary RT for pts with stages I-III BC in four of nine Dutch Cancer Centers.	• N = 65,966; • Convenience sample from a nation-wide cancer registry of 4 out of 9 cancer centers, b/w 1997 and 2008; • Inclusion criteria – women with stages I-III BC; • Exclusion criteria – metastatic disease or unknown metastatic status; • A national BC treatment guideline: Recommends the use of RT according to tumor, stage, and surgery type. • Primary endpoints: Rates of primary RT and BCS.	• Overall, there was a significant increase in the use of primary RT ranging from 55%-61% (1997) to 58%-68% (2008) and confirmed by multivariate analyses (OR 0.5; 95% ci: 0.4, 0.5); • This was partly explained by a higher rate of BCS followed by RT in 87%-99% of cases, and a reduced rate of total mastectomy followed by RT in 26%-47% of cases; • Increasing age (especially >75 yrs) was assoc. with a reduced use of RT confirmed by multivariate analyses (OR ≥75 yrs vs <55 yrs: 0.1; 95% CI: 0.1, 0.2); • Regional variances were observed in the use of RT after BCS and mastectomy early in the study (1997), however this variance decreased over time (2008).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Cannot exclude selection bias; • Potential for confounding from pt.-specific preferences.

Table 6: Breast Cancer Treatment in the Elderly

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
22. Ebner, Hancke, Blettner, Schwentner, Wockel, Kreienberg, …& van Ewijk. (2015). Germany Retrospective cohort design Objective: To investigate the associations among tumor characteristics, guideline adherence, and outcome, and compare these associations b/w younger (yBCP) and older (oBCP) BC pts.	• N = 7732; • Convenience sample from a multicenter BC database, b/w 1992 and 2008; • Inclusion criteria – women who are yBCP (50 – 69 yrs) vs. oBCP (⩾70 yrs); • Exclusion criteria - <50 yrs, those with missing data; • A national consensus guideline: Recommends treatment based on intrinsic subtype of BC. • Primary endpoint: DFS, OS, and guideline adherence in BC.	• oBCP had significantly higher tumor stages ($p < 0.001$), higher numbers of positive LNs ($p = 0.001$), and more hormone receptor-positive tumors ($p = 0.001$). oBCP also had lower tumor grading ($p = 0.001$) and less frequent HER2neu overexpression ($p = 0.003$); • Analysis found that any nonguideline-adherent treatment (or guideline violation) was significantly more common in oBCP than in yBCP ($p < 0.001$; • Nonguideline-adherent treatment is assoc. with decreased DFS [(yBCP HR 1.752; 95% CI: 1.484, 2.069) (oBCP HR 1.702; 95% CI: 1.402, 2.066)] ($p = 0.815$) and OS [(yBCP HR 1.852; 95% CI: 1.518, 2.259) (oBCP HR 1.693; 95% CI: 1.392, 2.060)] ($p = 0.515$) in pts with BC independent of age.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias; • Confounding may occur due to lack of data regarding comorbidities which may have affected the subjective judgement of the physician leading to nonguideline-adherent treatment in oBCP; • Non-compliance to treatment may also be another confounding factor to affect results.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
23. Hancke, Denkinger, Konig, Kurzeder, Wockel, Herr, …& Krelenberg. (2010). Germany Retrospective cohort design Objective: To determine if non-adherence to treatment guidelines occurs for women aged ⩾70 yrs. and changes OS and DFS.	• N = 1922; • Convenience sample from a specialized multi-center BC database b/w 1992 and 2005, comparing pts aged 50 - 69 yrs to pts aged ≥ 70 yrs (stratified into three groups: 70 – 74 yrs, 75-79 yrs, and ≥ 80 yrs); • Inclusion criteria - women ⩾50 yrs. with invasive BC; • Exclusion criteria – contralateral BC, in situ disease, metastatic disease, neoadjuvant CT, and age < 50 yrs.; • St. Gallen consensus/German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: DFS, OS	• Women > 70 yrs. less often received recommended BCS (70-79 yrs.: 74%-83%; > 79 yrs.: 54%) than women aged ⩽ 69 yrs. (93%); • Non-adherence to guidelines on RT (< 70 yrs.: 9%; 70-79 yrs.: 14%-27%; >79 yrs.: 60%) and CT (<70 yrs.:33%; 70-79 yrs.: 54%-77%; >79 yrs.: 98%) increased with age; • Omission of RT significantly decreased OS (⩽ 69 yrs.: HR = 3.29; *P*<0.0001; ⩾70 yrs.: HR 1.89; $p = 0.0005$) and DFS (⩽69 yrs.: HR 3.45; $p < 0.0001$; ⩾70 yrs.: HR 2.14; $p < 0.0001$). • OS and DFS did not differ significantly for adherence to surgery, CT, or ET.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias; • Potential confounding factors included lack of knowledge regarding comorbidities, and frailty.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
24. McCormick, Ottesen, Hughes, Javid, Khan, Mortimer, …& Edge. (2014). USA Retrospective cohort design Objective: To analyze changes in patterns of treatment among older women within NCCN institutions before and after a guideline change.	• N = 1292; • Convenience sample from a multicenter BC database, b/w 2000 - 2004 and 2005 - 2009; • Inclusion criteria - women ⩾70 yrs with stage I (T1 N0) hormone receptor-positive BC treated with BCS; • Exclusion criteria – had tumor > 2 cm, mastectomy, no surgery, hormone receptor-negative, positive LNs, received systemic CT, ET, or both (including RT before surgery), and f/u of <365 days after diagnosis; • NCCN guideline (2004): Recommends omitting RT after BCS for women ⩾ 70 yrs with stage I ER+/PR+ BC, who receive ET. • Primary endpoint: Rate of RT use in BC after BCS.	• Overall, 1005 (78%) received RT and 287 (22%) did not; • RT was omitted in 17% before guideline change and 26% omitted after; • When stratified by age groups, omission of RT was significantly assoc. with older age, specifically age ≥80 yrs [(OR 80-84 yrs: 3.35; 95% CI: 2.12, 5.30) (OR 85+ yrs: 9.04; 95% CI: 5.04, 16.21)] (p < 0.0001); • RT also more likely to be omitted for those without axillary surgery, smaller tumor size, and those with higher comorbidity scores. Also, more likely to omit RT in those who received ET alone, compared to those who received CT; • Wide variation among NCCN institutions in omission of RT (7% - 51%).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Potential for selection bias; • Individual provider biases and interpretation of clinical trial findings may create a confounding factor.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
25. Van Ewijk, Wockel, Gundelach, Hancke, Janni, Singer, …& Schwentner. (2015). Germany Retrospective cohort design Objective: Clinical trials are largely unavailable to pts > 65 yrs, therefore an evaluation of whether guideline-adherent adjuvant treatment is an equal alternative for this cohort is undertaken.	• N = 4142; • Convenience sample from a BC specialized multicenter database b/w 1992 and 2008; • Inclusion criteria – women (< 65yrs vs. 65-80 yrs) with primary invasive BC; • Exclusion criteria – bilateral BC, in situ disease, metastatic disease, phylloides, occult disease, those with incomplete f/u, unknown study participation status, unknown guideline conformity, receiving NAC, missing data on covariates; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS, and rate of guideline-adherent adjuvant treatment in BC.	• 23.2% were < 65 yrs and 76.8% were 65-80 yrs; • Pts ≥65 yrs were significantly more likely to have positive LNs, higher tumor grades, lower endocrine responsiveness, and higher rates of HER2 overexpression, while elderly (65-80 yrs) had significantly more co-morbidities and more favorable tumor biologies; • Pts ≥65 yrs not enrolled in clinical trials demonstrated a significantly inferior RFS (HR = 1.67; $p < 0.001$) and OS (HR = 1.98; $p < 0.001$) compared to clinical trials participants < 65.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Missing comorbidity data may create selection bias; • Confounding factors may affect outcomes.

Table 7: Molecular Profiling

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
26. Chen & Li. (2015). USA Retrospective cohort design Objective: To utilize newly available data to characterize racial/ethnic differences in cancer stages and treatment patterns across BC subtypes using a nationally representative sample.	• N = 102,064; • Convenience sample from multiple cancer registries, b/w 2010 and 2011; • Inclusion criteria - women ⩾ 20 yrs with primary invasive BC and known stage, hormone receptor and HER2 status; • Exclusion criteria – unknown HER2 or hormone receptor status, unknown cancer stage, unknown race/ethnicity; • NCCN guideline: Recommends the same primary treatment (total mastectomy, or BCS with RT) for women (< 70 yrs with stage I/II disease and tumors <2.0 cm) meeting those criteria regardless of their ER, PR, and HER2 status. • Primary endpoints: BC risk and guideline concordant treatment according to hormone receptor/HER2 status.	• Overall, women of all other racial/ethnic groups had a 20% to 60% higher risk of stage II-IV BC compared to non-Hispanic whites; • African American women had 40% - 70% higher risks of stage IV BC across all four subtypes (OR 1.6; 95% CI: 1.4, 1.7); • American Indian/Alaska Native women had a 3.9-fold higher risk (OR 3.9; 95% CI: 1.7, 9.2) of stage IV TNBC; • African American and Hispanic whites were 30% - 40% [(OR 1.4; 95% CI: 1.3, 1.6) (OR 1.3; 95% CI: 1.2, 1.4), respectively] more likely to receive non-guideline concordant treatment for BC overall and across subtypes.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential risk for misclassification bias (e.g., race/ethnicity) or coding errors; • Missing data may create selection bias with excluded pts; • Variation in reporting, testing, and interpretation of tumor biomarkers b/w hospitals may have introduced misclassification errors; • These registries lack data on other aspects of BC care such as CT, ET, and trastuzumab use, as well as pt-related factors which may have contributed to observed disparities.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
27. Schreuder, Kuijer, Rutgers, Smorenburg, van Dalen, & Siesling. (2017). Netherlands Retrospective cohort design Objective: Assess the use and impact of gene expression profiles (GEP), using MammaPrint™ 70-gene signature, on adjuvant CT national guidelines according to clinical high or low risk.	• N = 26,425; • Convenience sample from a national cancer registry b/w the years of 2011 to 2014; • Inclusion criteria – women with ER+ early BC (stratified as low-risk or high-risk); • Exclusion criteria – prior hx of malignancy or adjuvant CT; >70 yrs; pts who guideline already advises use of GEP as an adjunct to guide adjuvant treatment decisions; • National Dutch guideline: Recommends use of GEP in early BC pts, in whom benefit of CT is uncertain. • Primary endpoints: Rates of GEP testing in accordance with guideline recommendation in adjuvant CT treatment decision-making.	• Overall, 68.5% of pts with discordant clinical and genomic risk estimation were treated in line with the GEP test result; • GEPs assigned 20.3% of clinical low-risk pts to a high genomic risk category; • GEP use was independently associated with an increased risk of receiving CT in clinical low-risk pts (OR 2.12, 95% CI: 1.44, 3.11); • GEPs assigned 35% of clinical high-risk patients to a low genomic risk category; • In clinical high-risk pts who received a GEP, a low-risk GEP result was strongly associated with a decreased risk of CT administration (OR 0.05, 95% CI: 0.03, 0.07).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors. • Potential for selection bias; • Despite a multivariable logistic regression analysis, confounding by indication cannot be ruled out.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
28. Schwentner, Wockel, Konig, Jasnni, Boner, Blettner, …& Van Ewijk for the Brenda study group. (2013). Germany Retrospective cohort design Objective: To compare survival in pts with triple negative BC (TNBC) to those with other BC subtypes (non-TNBC).	• N = 9156; • Convenience sample from a specialized multi-center BC database b/w 1992 and 2008; • Inclusion criteria – women with invasive BC; • Exclusion criteria – in situ disease, metastases, bilateral BC, primary occult disease, phylloides tumor, incomplete f/u, unknown HER2 status or ER/PR status, or missing data on chosen variables; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoint: DFS, OS.	• 844 pts (9.2%) had TNBC; • TNBC demonstrated significantly decreased OS (HR 1.92; $p < 0.001$) and DFS (HR 1.53; $p < 0.001$) than non-TNBC; • TNBC pts aged $\geqslant$ 65 yrs had a significantly worse OS (HR 0.31; $p < 0.001$) and DFS (HR 0.42; $p < 0.001$) compared to TNBC pts aged 50-64; • Guideline adherence was significantly lower in all age groups of TNBC pts compared to non-TNBC pts ($p < 0.001$); • TNBC pts in all three age groups who were treated by guidelines had a better OS and a better DFS.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data; • Selection bias is always a fundamental risk with non-randomized data; • Potential for confounding factors.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
29. Schwentner, Wolters, Koretz, Wischnewsky, Kreienberg, Rottscholl, & Wockel. (2012). Germany Retrospective cohort design Objective: To analyze the assoc. b/w guideline-adherent adjuvant treatment and survival outcomes in TNBC by investigating the impact of different guideline-adherent therapies for TNBC on survival.	• N = 3658; • Convenience sample from a specialized multi-center BC database b/w 2000 and 2005; • Inclusion criteria – women with invasive BC; • Exclusion criteria – in situ disease, metastatic disease, bilateral BC, occult disease, and those with incomplete f/u; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS.	• 10.1% (371) pts had TNBC; • Compared to hormone receptor-positive/HER2-BC (p = 0.001) (HR 1.75; 95% CI: 1.27, 2.40), the recurrence rate of TNBC was significantly higher (p < 0.001) (HR 2.86; 95% CI: 2.17, 3.76); • 5-yr RFS and OS was significantly lower in TNBC [RFS: 74.8% (95% CI: 68.8-80.8%) vs 86.5% (95% CI: 84.6-88.4%) (log-rank p = 0.0001)] [OS: 75.8% (95% CI: 69.9-81.8%) vs 86.0% (95% CI: 84.1-87.9%) (log-rank p = 0.0001)]; • Overall, 66.8% TNBC were found with one or more (18%) guideline violations, which subsequently impaired OS and RFS (with RT and CT having the most important impact on survival).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data; • Selection bias is always a fundamental risk with non-randomized data; • Potential for other unknown confounding factors;

Table 8: Staging Investigations

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
30. Hahn, Tang, Lee, Munoz-Plaza, Adesina, Shen, …& Gould. (2015). USA Retrospective cohort design Objective: To evaluate and compare use of imaging for staging of breast cancer in two integrated health care systems (i.e., KP and IH).	• N = 10,010; • Convenience sample from tumor registries and EMRs of two regional health care systems, b/w 2010 and 2012; • Inclusion criteria - women with stages 0 to IIb BC; • Exclusion criteria – history of previous cancer diagnosis (except non-melanoma skin cancers); • NCCN/CCO/AHS/ASCO and Choose Wisely campaign guidelines: Recommends against use of advanced imaging for staging of early BC. • Primary endpoint: Rate of unnecessary staging imaging in early-stage BC.	• Overall, at least 15% of pts (1480) received at least one imaging test, with no statistically significant differences b/w the two regions; • Cat scan was most commonly used imaging modality (73%); • Close to half (48%) of all imaging tests were performed for diagnostic purposes; • 55% of imaging at KP were considered diagnostic while only 33% at IH.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size over geographically distinct regions; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Included data from only three of the seven KP regions, so potential for selection bias and misclassification error; • Only had a small number of chart abstractions (16%) in pre-surgical imaging and did not investigate other imaging services which may create confounding; • Generalizability of results may be limited due to large integrated health care systems.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
31. Han, Hogeveen, Goldstein, George, Brezden-Masley Hoch, …& Simmons. (2012). Canada Retrospective cohort design Objective: To assess consistency of radiological staging in an academic community oncology setting with standard guidelines and to determine the overall impact of non-adherence.	• N = 231; • Convenience sample from pt. records of a single institution b/w 2009 and 2010; • Inclusion criteria – women with stage I - III BC who had received diagnosis and surgery at the study institution; • Eligibility criteria – recurrent BC, in situ, or stage IV, primary surgery or oncology referral to other institutions; • CCO guideline: Recommends stage I – no staging investigations, stage II – bone scan only, stage III – chest/abdominal imaging and bone scan. • Primary endpoints: Rates of over-staging and guideline adherence.	• 55% (129) of pts underwent unnecessary investigations according to guideline; • 59% of stage I and 58% of stage II pts were over-investigated; • Distant metastases at time of dx was found in 1.3%, all of whom all had stage III disease; • Estimated cost of non-adherence is approx. $78 Canadian per early-stage BC pt.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size; • Canadian provincial study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data; • Single institution studies may not be generalizable; • Potential for selection bias by eliminating those who may have received diagnosis and surgery at different settings; • No discussion of statistical calculations or study limitations; • Potential for confounding factors such as determining whether imaging for staging or diagnostic purposes.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
32. Simos, Catley, van Walraven, Arnaout, Booth, McInnes, …& Clemons. (2015). Canada Retrospective cohort design Objective: To determine whether practice patterns in Ontario conform with the guideline recommendation to not perform imaging to detect metastatic disease in the majority of pts with early-stage BC, who are asymptomatic.	• N = 26,547; • Convenience sample from a provincial cancer registry linked to a hospital database b/w 2007 and 2012; • Inclusion criteria – women with early-stage (stage I – II) invasive BC; • Exclusion criteria – prior BC diagnosis, stages 0/III/IV disease, null/unknown stage disease, DCIS, LA or inoperable disease; • CCO guideline: Recommends no imaging for stage I and a bone scan for stage II disease for staging of early BC pts. • Primary endpoints: Rate of inappropriate staging imaging in early-stage BC.	• 85.9% (22,811) had at least one imaging test for distant metastatic disease, with a total of 83,249 imaging tests performed (mean of 3.7 imaging tests per pt); • Despite guidelines (CCO and ASCO) recommending no imaging for asymptomatic, stage I and II pts, imaging was performed in 79.6% and 92.7% of cases, respectively; • Of all imaging tests, 23.8% were classified as confirmatory investigations (additional imaging test performed on a body site that had already been imaged); • Imaging more likely for younger pts, those with more comorbidities, higher grade/stage tumors, undergone pre-op breast ultrasound, mastectomy or surgery in the community setting.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large representative sample size; • Multicenter study; • Canadian provincial study (results may be more likely to be comparable and relatable to other Canadian provincial studies). <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data to determine specific indication for imaging; • Potential confounding since data did not allow determination of symptomatology timeline.

Table 9: Breast Cancer Characteristics

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
33. Schwentner, Wolters, Wischnewsky, Kreienberg, & Wockel. (2012). Germany Retrospective cohort design Objective: To examine survival parameters in pts with bilateral (BBC) vs unilateral (UBC) unifocal BC, and treatment patterns and their influence on guideline adherence on pt. survival.	• N = 5292; • Convenience sample from a specialized multi-center BC database b/w 2000 and 2005; • Inclusion criteria – women with either BBC or UBC; • Exclusion criteria – in situ disease, metastatic disease, bilateral BC, occult disease, and those with incomplete f/u; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS.	• 4.3% (229) pts had BBC and 95.7% (5063) had UBC; • No significant difference b/w different hospitals in terms of guideline adherence; • Pts with BBC were found to have a significant inferior RFS ($p < 0.001$) (HR 1.89; 95% CI: 1.46, 2.45) compared to UBC even after adjusting for tumor size, nodal status and grading ($p = 0.022$) (HR 1.39; 95% CI: 1.05, 1.85); • OS was also significantly impaired for BBC pts ($p = 0.004$) (HR 1.55; 95% CI: 1.15, 2.07) though this was not significant after adjusting; • Only 15.7% of pts with BBC were treated with 100% guideline-adherence; • Outcome decreases significantly with the # of guideline violations.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data; • Selection bias is always a fundamental risk with non-randomized data; • Potential for other unknown confounding factors.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
34. Wolters, Wockel, Janni, Novopashenny, Ebner, Kreienberg, …& Schwentner. (2013). Germany Retrospective cohort design Objective: To investigate the impact of multicentric (MC)/multifocal (MF) BC, and whether current validated guidelines present effective treatment recommendations to improve outcomes for these subtypes of BC.	• N = 8935; • Convenience sample from a specialized multi-center BC database b/w 1992 and 2008; • Inclusion criteria – women with invasive BC having unifocal (UF), MC, or MF tumors; • Exclusion criteria – in situ disease, metastatic disease, bilateral BC, occult disease, phylloides, and those with incomplete f/u; • German national consensus guideline (S3): Recommends specific loco-regional and systemic treatment decisions based on tumor-related factors. • Primary endpoints: RFS, OS.	• 79.2% (7073) had UF tumors, 15.6% (1398) had MF, and 5.2% (464) had MC; • Compared to UF BC, RFS was significantly worse for pts with MC [RFS $p = 0.019$; HR 1.38 (95% CI: 1.06, 1.80)] and pts with MF [RFS $p = 0.007$; HR 1.25 (95% CI: 1.06, 1.48)]; • OS was also significantly worse for MC pts [OS $p = 0.001$; HR 1.46 (95% CI: 1.16, 1.83)] but no significant difference found in OS b/w MF and UF BCs [OS $p = 0.321$; HR 0.92 (95% CI: 0.79, 1.08)]; • Guideline adherence was significantly lower in pts with MF (n=580; 41.5%) and MC (n=204; 44.0%) compared to pts with UF (n=3871; 54.7%) ($p < 0.001$) tumors; • Guideline violations were assoc. with a highly significant deterioration in RFS and OS throughout all subgroups except MC.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing information; • Selection bias is always a fundamental risk with non-randomized data; • Potential for confounding factors.

Table 10: Axillary Lymph Node Evaluation

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
35. Chong, Walters, de Silva, Taylor, Spillane, Kollias, … & Maddern. (2013). Australia/New Zealand Retrospective cohort design Objective: To examine the patterns of ALND after SNB in women treated for early-stage BC.	• N = 14,879; • Convenience sample from a national multi-center BC surgery database b/w 2006 and 2010; • Inclusion criteria – women with invasive BC, either ⩽3 cm or >3 cm; • Exclusion criteria – those with missing data, or had received NAC; • Cancer Australia/New Zealand treatment guidelines: Recommends SNB as valid alternative to ALND when BC tumor ⩽3 cm; ALND when SN is positive; observe axilla only if SNB is negative. • Primary endpoints: rates of ALND after positive and negative SNB.	• For those with tumors ≤3 cm, 24.1% had at least one pos. SN (only 78.7% of these underwent ALND). The remaining 75.9% had a neg. SN, though 9.6% went on to have ALND; • For those with tumors >3 cm, half had a pos. SN with 15.3% not undergoing ALND. While 21% of pts with a neg. SN went on to have ALND; • Only pts age >70 yrs was statistically significant favoring SN pos. pts not proceeding to second surgery ($p < 0.001$) (OR 2.3; 95% CI: 1.6, 3.3); • Among pts with an neg. SN result, those with >3cm tumors ($p < 0.001$), higher tumor grade ($p = 0.006$), dx of LVI ($p = 0.008$) and age <40 yrs ($p = 0.01$) were more likely to proceed to ALND.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Selection bias is always a fundamental risk with non-randomized data; • Potential for confounding due to individual health provider biases and interpretation of clinical trial findings.

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
36. Mitchell, Lin, Shen, Colfry, Kuerer, Shaitelman …& Bedrosian. (2017). USA Retrospective cohort design Objective: To analyze all surgical approaches to axillary evaluation in pts with DCIS.	• N = 88,083; • Convenience sample from a national cancer data base b/w 1998 and 2011; • Inclusion criteria – women with DCIS who either underwent mastectomy or BCS; • Exclusion criteria – history of prior cancer, received chemotherapy, insurance status unknown, treated at other specified types of cancer programs; • NCCN/ASCO guidelines: Recommends the use of SNB, not ALND for the surgical management of DCIS, in the absence of invasive cancer or proven axillary disease. • Primary endpoint: Rates of SNB or ALND in DCIS.	• 37% (31,912) of pts underwent total mastectomy while 63% (55,349) had BCS; • The use of SNB for mastectomy increased from 24.3% to 77.1%, while ALND decreased from 50.0% to 16.3% ($p<0.01$); • The use of SNB for BCS increased from 7.2% to 39.4%, and ALND decreased from 12.9% to 4.5% ($p<0.01$); • On multivariate analysis, those who underwent total mastectomy at community cancer program were less likely to have an axillary examination compared to an academic/research program [OR 0.63 (95% CI: 0.54, 0.75)] and [OR 0.84 (95% CI: 0.76, 0.93)], respectively; • Facility type and location were also significant for those who underwent BCT.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors due to missing data on use of NAC; • Selection bias is always a fundamental risk with non-randomized data; • Does not account for patient-related factors such as treatment preference.

Table 11: Immediate Breast Reconstruction

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
37. Van Bommel, Mureau, Schreuder, van Dalen, Vrancken-Peeters, Schrieks, ,,, & Siesling. (2017). Netherlands Retrospective cohort design Objective: To evaluate the use of immediate breast reconstruction (IBR) after mastectomy for invasive BC and DCIS and determine whether any variation is associated with pt and tumor factors.	• N = 16,953; • Convenience sample from a national multicenter BC database, from 2011 to 2013; • Inclusion criteria – women with either DCIS or invasive BC; • Exclusion criteria – presence of metastatic disease, non-mastectomy surgical interventions; • National Dutch/NICE guidelines: Recommends considering IBR in all pts who undergo mastectomy. • Primary endpoint: IBR rates for invasive BC and DCIS.	• On average 16.8% (2536) of pts with invasive BC underwent IBR, while 42% (786) of those with DCIS had IBR; • For invasive BC, younger pts (<50 yrs) utilized IBR more frequently (OR 1.73; 95% CI: 1.58, 1.91) compared to 50-65 yrs age group. Used less often in those with large tumors and/or involved lymph nodes; • For DCIS, younger age and multifocality significantly increased IBR rates. Older age (≥65 yrs) had a OR of 0.16 compared to pts 50-65 yrs, while pts with multifocal disease had a 1.56-fold higher chance of undergoing IBR compared to those with unifocal tumors (95% CI: 1.22, 1.99); • After adjustments, variation in use of IBR b/w hospitals remained large.	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Very large sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors. • Registration (selection) bias may be present which may also create misclassification error; • Does not account for confounding pt-related factors, such as preference, lack of knowledge, beliefs of physicians/surgeons, or hospital-related factors (urban vs rural, availability of a plastic surgeons).

Table 12: Genetic Referrals

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
38. Stuckey, Febbraro, Laprise, Wilbur, Lopes, & Robison. (2016). USA Retrospective cohort design Objective: To evaluate the referral patterns for genetic counseling and testing of women with an history of BC diagnosis who are < 50 yrs.	• N = 314; • Convenience sample from an institutional tumor registry and a chart review from an academic oncology program b/w 2004 and 2010; • Inclusion criteria – women ≤ 50 yrs without a documented BRCA mutation, who meet the eligibility criteria for high risk; • Exclusion criteria – those who did not meet the eligibility criteria for high risk; • NCCN guideline: Recommends that pts who meet the eligibility criteria should trigger referral for genetic counseling (BC diagnosis at ⩽50 yrs, TNBC, ≥2 BC primaries in one individual, male BC, Aahkenazi Jewish descent, and BC at any age with family history of breast and/or ovarian cancer). • Primary endpoint: Rates of genetic counseling referral for high risk pts (⩽ 50yrs).	• An overall referral rate of 34.1% (107 of the 314 women) indicated a suboptimal referral to genetic counseling (but did increase over time); • 77.6% of those referred received counseling and 95.2% underwent genetic testing (16.5% had a BRCA mutation); • Women with a suspicious family history were more likely to be referred (67.3% vs 36.2%; $p <$ 0.0001); • Women who chose prophylactic contralateral mastectomy also were more likely to be referred (63.6% vs 36.4%; $p <$ 0.0001).	Strength of Study Design: Moderate Quality of the Study: Medium Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size. <u>Limitations</u> • Potential for coding errors; • Misclassification error and/or selection bias may have been introduced if pts received genetic counseling/testing elsewhere, or from missing data when referrals may not have been charted; • Differences in pre-existing guidelines (other than NCCN) and changes at a program level may have resulted in larger number of referrals which could create confounding. • Single institution studies are not as generalizable has those from multicenter studies.

Table 13: Follow-up Guidelines

Author(s), Country, Study Design & Objective	Sample & Methods	Key Results and Findings	Strengths/ Limitations
39. Grandjean, Kwast, de Vries, Klaase, Schoevers, & Siesling. (2012). Netherlands Retrospective cohort design Objective: To evaluate adherence with f/u criteria as suggested by a national guideline and to determine the factors that influence the adherence to the guideline.	• N = 196; • Convenience sample from a national cancer registry database in 2003; • Inclusion criteria - women with invasive BC treated in 2 hospitals; • Exclusion criteria – metastatic disease, or a contralateral BC; • A national guideline: Recommends f/u care for 5 years (physical exam four times in 1st yr, twice in 2nd yr, and annually thereafter), and annual mammogram. • Primary endpoints: Rates of completion of 5 yr f/u, a disease relapse, death, or lost to f/u.	• A total of 54 pts did not complete the full 5 yrs of f/u; • In the first yr, pts visits were fewer than recommended; • In 2nd to 5th yrs, visits were more often than recommended (nearly double) (p<0.05), and was assoc. with receipt of RT (p<0.01); • Physical exams performed during 97% of visits but mammograms were performed slightly less than recommended.	Strength of Study Design: Moderate Quality of the Study: Low Directness of Evidence: Extrapolation <u>Strengths</u> • Moderate sample size; • Multicenter study. <u>Limitations</u> • Potential for misclassification bias or coding errors; • Losing 28% of the study population will likely introduce confounding of results; • Sample size may affect external validity; • Potential for confounding factors.

Appendix C: Consultations Summary Report

ADHERENCE TO AN ONCOLOGY CLINICAL

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April 14, 2018

This practicum project will provide an opportunity to conduct a program evaluation on how often surgeons in Newfoundland and Labrador (NL) utilize the services of medical oncology to discuss the option of neoadjuvant therapy for patients diagnosed with locally advanced or inflammatory breast cancer. This program evaluation will also help determine whether these surgeon referrals are being made in concordance with the Eastern Health Breast Disease Site Groups' (BDSG) clinical practice guideline "Neoadjuvant Treatment of Primary Breast Cancer" (2014). A comprehensive literature search and summarization of the research findings has been completed. The highlights of the most common methodologies and strategies utilized in the field of breast cancer for evaluating evidence-based oncology guideline adherence. The next step outlined in the practicum proposal was to carry out a series of consultations with key individuals within the organization, at the Dr. H. Bliss Murphy Cancer Center (DHBMCC), who have the expertise necessary to aid in the development of an evaluation plan to obtain the desired data.

Methods

The consultation process will permit the investigator to avail of the expertise of others to achieve the following objectives necessary to successfully develop an evaluation plan. These objectives were:

1. To develop appropriate eligibility criteria using inclusion and exclusion criteria for patients newly diagnosed with either locally advanced or inflammatory breast cancer;
2. To identify factors which may affect the surgeons' decision-making for choice of primary treatment modality in locally advanced or inflammatory breast cancer; and

3. To assess the feasibility of obtaining the required data from the cancer registry database and patients' medical records.

Setting and Sample

The setting chosen was the DHBMCC where all but one of the key individuals worked. These individuals were all colleagues and co-workers of the investigator and with whom a rapport has already been established. The meeting with each individual took place in their own offices, face-to-face with the exception of one which was carried out via telephone. This allowed each of the individuals to feel at ease in their own space and each office provided comfortable seating for all. Finally, each office was also equipped with a door to provide both a quiet and private environment in which to meet.

Four of the five individuals were healthcare professionals while the remaining one was a certified cancer registrar. These individuals were chosen for consultation due to their years of expertise in their field and were deemed to be experts. Two of the individuals were medical oncologists, who specialize in the field of breast cancer treatment and management. One was a general surgeon who routinely performed breast surgery for patients with breast cancer and was also a member of the Eastern Health BDSG. The divisional manager of the cancer registry was consulted to help determine whether it was feasible to obtain the data needed to perform this evaluative process. Finally, the ARIA computer system clinical support person was interviewed to discuss the various computer systems that would need to be accessed to obtain data from individual patient medical records.

Data Collection, Management and Analysis

Data Collection. Though this project is a quantitative evaluation study, it is not unusual for such a study to have a qualitative component. In this case, valuable information was required from the key individuals necessary to move forward with this project and the decision was made to use interviews to obtain it. To accomplish this, a list of open-ended questions was generated for each interviewee. These questions were formulated not just to obtain specific answers but to also allow the respondent the opportunity to provide context and detail to his/her replies. A list of the questions used have been added to Appendix A of this report. Notes were taken during the interviews without the use of tape recording to allow respondents to speak freely. Each respondent(s) was asked a different set of questions necessary for providing the specific information being pursued.

The general surgeon was interviewed via telephone while the remaining respondents were interviewed face-to-face. A semi-structured question and answer interview was conducted for each separately, with the exception of the two medical oncologists who were interviewed together. Prior to beginning each interview, the individual was informed of the purpose of the evaluation and how the information provided would be used. Once the interviewer had exhausted the list of questions, the key aspects of the discussion were summarized by the interviewer to ensure the interpretation was correct. The individuals were thanked for their participation and advised that the findings of the evaluation will be available in a PowerPoint presentation for staff and/or in an oral report delivered to the BDSG at the end of the practicum. The interviews took

place during working hours (i.e., 8:30 am to 5:00 pm) at a time convenient for the interviewees. The interviews were between 20 to 40 minutes in length.

The medical oncologists were asked to develop appropriate eligibility criteria (i.e., inclusion and exclusion criteria) for patients diagnosed with locally advanced or inflammatory breast cancer, how to define the control and experimental groups, and what years should be studied to determine guideline adherence outcomes. In addition, they were also asked to identify factors that may influence decision-making about treatment sequencing. Interviewing the two oncologists together permitted an opportunity for the physicians to reach a consensus on the eligibility criteria best suited for the purposes of the program evaluation.

Once an explanation of the project was provided, the cancer registrar was asked whether it was feasible to collect the data required through the cancer registry database. In addition, the registrar was asked whether patients who had received neoadjuvant therapy were identified in the database, as well as how to access the patient/tumor/facility-related variables of interest. Next, the computer clinical support person was asked about how to assess data not available in the cancer registry database. A new computer system (i.e., ARIA) had been introduced during the time covered by the evaluation; it was important to determine how to access the data, depending on the year of study under investigation. Being unfamiliar with the operation of the ARIA system, the assistance of the clinical support person will be extremely helpful in navigating an unfamiliar computer database.

The telephone interview with the general surgeon was performed at the beginning of N6661 due to timing conflicts in meeting during the latter weeks of N6660.

Approximately two weeks prior to the interview, the surgeon had been emailed a description of the project's purpose, how the information gained would be of benefit, as well as a list of patient- and tumor-related factors which may affect the surgeon's decision as to whether a patient may be a candidate for neoadjuvant therapy. This list which is located in Appendix A, had been generated from the previously conducted literature review and the survey results of surgeons in a research study carried out by Mamounas et al. (2016). This interview was highly valuable in defining which patient/tumor factors are deemed most important to consider in determining whether a medical oncology referral was warranted for the consideration of neoadjuvant therapy.

Data Management and Analysis. After each interview was completed, the notes taken were typed and saved in a Word document format. Inside this document, each respondent was given a unique identifier. The content of the interview notes was analyzed, summarized and are included in this report. Since each interviewee, except for the two medical oncologists, were asked very different questions it was impossible to synthesize the answers. This is usually a technique reserved for identifying themes or patterns in the responses of several participants in a qualitative research study who had been asked similar questions. The interview with the medical oncologists was conducted with them together and prevented synthesis since its focus was more consensus-based. Therefore, it was more appropriate to summarize the responses and arrange it in a clear, concise manner in order to allow for the achievement of those objectives outlined earlier in the report.

Ethical Considerations

A meeting with the program director of the provincial cancer care program was arranged to discuss the practicum proposal and its topic. The project will require access to the cancer registry database as well as the electronic patient health records, and we discussed whether an ethics review board approval would be necessary. The program director agreed that this was clearly an evaluation of a pre-existing health service by a staff member and should be exempt from ethics review board approval. The Newfoundland and Labrador's Health Research Ethics Authority screening tool was completed and can be found in Appendix B. The results indicate that the most probable purpose of the project is for a quality improvement or evaluation function. The program director granted permission to proceed with the evaluation project, including permission to access both the cancer registry database and electronic patient health records.

The privacy and confidentiality of the individuals who agreed to be interviewed for these consultations was protected by using a unique identifier in the notes taken at the interviews. There is no direct personal identification of these individuals in any of the reports needed for this practicum project. The only direct identification of these individuals would be in a practicum proposal document, shared between only my supervisor and myself, and will be kept securely in a password protected computer system, within a locked office at the DHBMCC. All individuals volunteered to be interviewed or did so as a part of their job descriptions. Consent was not specifically requested though all individuals agreed to participate.

Results

The results are presented according to who were consulted. These are individual(s) from:

Medical Oncology. The consultation began with a series of questions for the medical oncologists to help isolate the exact group of patients necessary for the project. The following summary is meant to reflect the content of the ensuing discussion. The first objective of this consultation was to decide what patients should be included in this evaluation. Though historically neoadjuvant therapy had been used primarily in the presence of locally advanced disease and inflammatory breast cancer, its use in the management of early-stage operable breast cancer for those who desire breast conserving surgery is gaining in popularity. However, both physicians believed that insufficient data would be available in this province for a cohort of patients with early stage breast cancer where neoadjuvant therapy would be used to facilitate breast conservation. Over the years, both physicians have triaged newly referred breast cancer cases, and neither could recall even one case of a neoadjuvant referral for the intent of breast conserving measures. They felt that this was probably related to the lack of available surgeons with specialty-training in breast cancer management in this province, since the overwhelming majority tend to be general surgeons. Therefore, the decision was made to focus primarily on the locally advanced and the inflammatory breast cancer population only.

The discussion next centered on how to best to stratify the study population in order to evaluate how often surgeons utilize the referral process for the medical oncology discipline, intended for neoadjuvant treatment purposes. The physicians agreed that the best approach was to divide the eligible study population into two groups, which

consisted of those referred to medical oncology for neoadjuvant consideration (i.e., had received chemotherapy and/or endocrine therapy first) and those not referred (i.e., had received surgery first). Each of two groups will be further stratified according to diagnosis, either has having a locally advanced breast cancer or an inflammatory breast cancer.

The next topic concerned the eligibility criteria of the patients who should be chosen to represent the study population of interest for this evaluation. The physicians concluded that the specific eligibility criteria for locally advanced breast cancer and inflammatory breast cancer should be in accordance with the American Joint Committee on Cancer (AJCC) Staging manual, 7^{th} ed., (2010). Therefore, all women with pathologically-confirmed, clinically measured tumors ≥ 5 cm in size and/or significant lymph node involvement [including stage IIB (T3N0 only) and all stage IIIs], which are inoperable or where it's questionable whether clear margins can be achieved, are deemed to have locally advanced breast cancer. The eligibility criteria for inflammatory breast cancer will be all women with a pathologically-confirmed diagnosis and a defined clinical appearance of erythema and edema (peau d'orange). The physicians also suggested that the exclusion criteria should be those with in situ disease only; those with metastatic disease at diagnosis; male breast cancers; or those diagnosed with breast cancer, having any stages other than those listed in the inclusion criteria.

This evaluation is also concerned with whether the Eastern Health's BDSG guideline had an impact on surgeons' utilization of medical oncology referrals for neoadjuvant therapy discussion. The medical oncologists were advised that the plan is to evaluate the neoadjuvant referral rate for a year prior to the implementation of the

guideline in 2014, and the year following. To reflect this intention, the two original groups (referred and non-referred) would be further stratified by year of study to assess the guideline's impact. The physicians agreed that 2013 was an appropriate choice for the pre-implementation year. However, they suggested that 2016 would be a better choice for the post-implementation year, due to the opinion that 2015 was deemed too early to accurately gauge guideline impact. Since the tumor registry data was unavailable for 2017, this eliminated this choice as a potential year of study.

The physicians noted that the reasons for referring patients with locally advanced or inflammatory breast cancer are often multi-factorial. They suggested that factors, such as patient demographics (e.g., age), tumor-related characteristics (e.g., histologic subtypes, clinical tumor stage, clinical nodal status, tumor grade, hormone receptor status), as well as physician-related (e.g., surgery type: lumpectomy, mastectomy) and hospital-related information (e.g., facility type, location) can all play a role in determining which patients will receive a consultation with a medical oncologist.

Provincial Cancer Registry. An explanation of the data desired was provided to the director of the cancer registry, and a discussion regarding the feasibility of obtaining it followed. The director explained that there may be some variation in what information could be provided according to year of study interest. This was due to the replacement of the OPIS computer system at the DHBMCC with the new ARIA electronic patient health record computer system in 2014. The ARIA system can be accessed by the cancer registry database while the OPIS computer could not. The director for the cancer registry will collect the data as requested from the registry database, insert it into an Excel spreadsheet format, and transfer its contents to the guardianship of the investigator.

It was decided that the pre-guideline implementation data will include all female patients diagnosed with breast cancer, meeting the outlined eligibility criteria, from January 1, 2013 to December 31, 2013, inclusive. The director clarified that since the ARIA system was not available in 2013, the tumor registry database at that time may not have access to all data related to the factors/variables of interest for this evaluation. Therefore, some of the data will likely have to be collected individually from the patient health records in the OPIS system, by the investigator. To assess the post-guideline implementation data, the eligible patients who were diagnosed from January 1, 2016 to December 31, 2016 will be identified, with most of the additional factors/variables data being available through the cancer registry database. However, any data not available will again be the responsibility of the investigator for its collection from the ARIA electronic health record.

The discussion continued regarding the specific patient/tumor/facility-related data that would be captured from the cancer registry database. The director advised that patient demographics, such as name, age at diagnosis, and MCP number would be collected, requiring de-identification which would be the responsibility of the investigator to perform. In addition, tumor characteristics (e.g., tumor size, histology, and lymph node status), names of referring surgeon/physician, type of surgery, and name and type of hospital/facility will also be collected from the database for each patient, upon request.

Information Technology. ARIA is the first paperless electronic patient health record at the DHBMCC and has been in service since 2014. It can integrate information from the hospital health information system, known as Meditech as well as allow in-hospital access to the medical records of oncology patients at the DHBMCC. The clinical support

staff confirmed that to access patient health records from 2013 will require using the OPIS system which is still computer accessible. However, this system still necessitates the user to access Meditech for radiology, pathology, and laboratory test results if this information is required. Any data needed from patient health records in 2016 will be available in ARIA. Though this system is both complex and has a steep learning curve, the clinical support person has agreed to provide instruction and mentoring in its use.

General Surgeon. The telephone interview began with a reiteration of the purpose of the evaluation project and the questions of interest to be asked. The first question asked was regarding which patient-related factors were most important in influencing a surgeon's decision-making in determining the sequencing of treatment. The surgeon agreed that a patient's health and co-morbidities, as well as the patient's preference for timing of surgery and level of interest in breast conserving surgery were all of equal value in the decision-making process. Although patient age was important, it played a lesser role in treatment decisions if the patient was of good health and had few co-morbidities.

The surgeon suggested that the initial tumor-related characteristics which would initiate a strong response to pursue a medical oncology referral for neoadjuvant therapy consideration would include evidence of locally advanced disease such as large tumor size of ≥ 5 cm in length of any dimension, involvement of the skin or chest wall involvement on clinical examination, and/or a pathological diagnosis of inflammatory breast cancer. The clinical presentation of axillary lymph node involvement is important but not always helpful in determining the level of lymph nodes involvement. Other features which may affect the surgeon's propensity to refer include histology and grade. Lobular carcinomas are known to be less aggressive than ductal carcinomas and

frequently are treated with surgery first. Well differentiated tumors are associated with a favorable prognosis (e.g., tubular, cribiform) and often are less likely to be referred to medical oncology than poorly differentiated which are associated with an aggressive nature and a poor prognosis (e.g., apocrine, metaplastic). Bilateral breast cancer as well as multifocal and/or multicentric disease may also play a role in influencing the surgeons' decision to refer.

A discussion then ensued regarding the research evidence which suggests that there is a survival advantage for molecular subtypes, such as triple negative and human epidermal growth factor receptor (HER2) positive breast cancers when these patients receive specific targeted neoadjuvant therapy. The surgeon acknowledged that this research has begun to change practice across the country and admitted that molecular subtyping, especially triple negative subtypes, has influenced his decision to refer patients to medical oncology as well. The question than arose whether surgeons should be requesting immunohistochemistry testing for estrogen/progesterone and HER2 receptors on all core biopsies of suspected locally advanced breast cancers. This surgeon suggested that some provinces provide hormone receptor and HER2 testing on all breast core biopsies regardless of size which would standardize the approach.

Finally, the surgeon was asked if there were any other characteristics or factors which weren't listed that he may feel was of equal importance in influencing the treatment sequence. The surgeon suggested that in extenuating circumstances the definition of locally advanced can be tumors < than 5 cm. For instance, when the patient has small breasts and though the tumor size may not meet the standard definition of locally advanced, the tumor itself may be locally advanced for that patient.

Conclusion

The consultation process provided the opportunity to accumulate the information needed to move forward with the development of an evaluation action plan. This process has created a clarity of how this practicum project can be achieved and has helped guide the investigator towards the identification of the next series of steps required to extract the data, safeguard its security and perform the analysis. The practicum project has begun to solidify and give shape to an idea which began merely as a notion discussed at a meeting. It is very exciting to see how the accomplishment of each activity, outlined in Nursing 6660, has combined to bring the investigator closer to the reality of finally developing and carrying out the evaluation plan. The end goal of which will be to help determine the status of the neoadjuvant referral and use for patients with breast cancer in this province and potentially inspire the necessary program adjustments to ultimately aid in improving outcomes for these patients.

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Appendix A

Questions for the medical oncologists:

1. What breast cancer patient cohorts should be included in this neoadjuvant referral evaluation project?
2. How should the eligible breast cancer population be stratified in terms of groups?
3. What are the specific inclusion and exclusion criteria which would describe the eligible sample population?
4. What year(s) should be reviewed and data extracted from the cancer registry to determine the rates of adherence before and after the implementation of the Eastern Health BDSG guideline?
5. What other data should be extracted from either the cancer registry and/or patients' medical records, which may aid in determining what variables influence surgeons to refer patients with locally advanced or inflammatory breast cancer, for neoadjuvant therapy consideration?

Questions for the director of the cancer registry:

1. Given the purpose for this evaluation project, is it possible to collect the data of all female patients who meet the eligibility criteria?
2. Is it possible to identify those patients who received a referral for neoadjuvant discussion or actually received neoadjuvant therapy?
3. Can patient/tumor/facility-related data be collected on each patient from the cancer registry database?

Questions for the ARIA clinical support:

1. What is the process to follow to obtain data from the patient health records for the years of 2013 and 2016?

Questions for the general surgeon:

1. What tumor-related characteristics would influence your decision to refer your patient with breast cancer to medical oncology for consideration of neoadjuvant therapy?
2. What patient-related characteristics would influence your decision to refer your patient with breast cancer to medical oncology for consideration of neoadjuvant therapy?
3. Are there other characteristics or factors not on the list that you personally deem to be important in considering the use of neoadjuvant therapy for your patients?

Patient-related and tumor-related characteristics/factors

- Skin/chest wall involvement;
- Tumor size;
- Histologic grade and type;
- Human epidermal growth factor receptor status;
- Estrogen and progesterone status;
- Inflammatory breast cancer;
- Clinical assessment of axillary lymph node involvement;
- Patient's age;
- Patient's health and comorbidities;

- Patient’s preference for timing of surgery; and
- Patient’s level of interest in breast conservation surgery.

Appendix B: Health Research Ethics Authority Screening Tool

	Question	Yes	No
1.	Is the project funded by, or being submitted to, a research funding agency for a research grant or award that requires research ethics review?	❒	☒
2.	Are there any local policies which require this project to undergo review by a Research Ethics Board?	❒	☒
	IF YES to either of the above, the project should be submitted to a Research Ethics Board. **IF NO** to both questions, continue to complete the checklist.	❒	☒
3.	Is the primary purpose of the project to contribute to the growing body of knowledge regarding health and/or health systems that are generally accessible through academic literature?	❒	☒
4.	Is the project designed to answer a specific research qu estion or to test an explicit hypothesis?	❒	☒
5.	Does the project involve a comparison of multiple sites, control sites, and/or control groups?	❒	☒
6.	Is the project design and methodology adequate to support generalizations that go beyond the particular population the sample is being drawn from?	❒	☒
7.	Does the project impose any additional burdens on participants beyond what would be expected through a typically expected course of care or role expectations?	❒	☒
LINE A: SUBTOTAL Questions 3 through 7 = (Count the # of Yes responses)		**0**	**7**
8.	Are many of the participants in the project also likely to be among those who might potentially benefit from the result of the project as it proceeds?	❒	☒
9.	Is the project intended to define a best practice within your organization or practice?	☒	❒
10.	Would the project still be done at your site, even if there were no opportunity to publish the results or if the results might not be applicable anywhere else?	☒	❒
11.	Does the statement of purpose of the project refer explicitly to the features of a particular program, organization, or region, rather than using more general terminology such as rural vs. urban populations?	☒	❒
12.	Is the current project part of a continuous process of gathering or monitoring data within an organization?	☒	❒
LINE B: SUBTOTAL Questions 8 through 12 = (Count the # of Yes responses)		**4**	**1**
	SUMMARY: Line B = 4 > Line A = 0 Quality/Evaluation **See Interpretation Below**		

Interpretation:

- If the sum of Line A is greater than Line B, the most probable purpose is **research**. The project should be submitted to an REB.
- **If the sum of Line B is greater than Line A, the most probable purpose is quality/evaluation. Proceed with locally relevant process for ethics review (may not necessarily involve an REB).**
- If the sums are equal, seek a second opinion to further explore whether the project should be classified as Research or as Quality and Evaluation.

These guidelines are used at Memorial University of Newfoundland and were adapted from ALBERTA RESEARCH ETHICS COMMUNITY CONSENSUS INITIATIVE (ARECCI). Further information can be found at: http://www.hrea.ca/Ethics-Review-Required.aspx.

NOTE: Since the YES answers are greater in Line B (4) than those in Line A (0), this indicates that this practicum project is likely to be a Quality Initiative or Evaluation Project.

Appendix D: Chart Review Report

ADHERENCE TO AN ONCOLOGY CLINICAL

Cynthia Higdon

Memorial University of Newfoundland

August 22, 2018

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List of Appendices

The overall objective of this program evaluation was to determine whether surgeons in the province of Newfoundland and Labrador (NL) were adhering to a multidisciplinary-developed oncology clinical practice guideline, developed by the Eastern Health Breast Disease Site Group (BDSG). The 2014 guideline "*Neoadjuvant Treatment of Primary Breast Cancer*" outlines which patients may be appropriate for neoadjuvant therapy (Eastern Health, 2014). This evaluation project will determine whether eligible patients, diagnosed with locally advanced or inflammatory breast cancer, are being referred to the services of medical oncology at the Dr. H. Bliss Murphy Cancer Center (DHBMCC) or any of its satellite clinics around the province of NL, for consideration of neoadjuvant treatment. A chart review has been chosen as the best option by which data can be collected to allow the comparison of neoadjuvant referral rates prior to and after the dissemination of the guideline in an attempt to establish whether guideline adherence has occurred. This report will provide an overview of the methods used in conducting the chart review process; outline the benefits and limitations of the retrospective chart review; discuss the measures taken to improve the rigor of the data collection process; and summarize the results and recommendations of this evaluation project.

Objectives

The primary aim of this evaluation was to determine how effective the Eastern Health Breast Disease Site Groups' (BDSG) guideline "*Neoadjuvant Treatment of Primary Breast Cancer*" (2014) had been in influencing surgeons and the corresponding rates of neoadjuvant referral to the medical oncology discipline for eligible patients with breast cancer. The objectives of this evaluation were to:

1. Compare the rates of patient referrals to the service of medical oncology for neoadjuvant therapy discussion pre- and post-guideline implementation; and
2. Identify the factors that are associated with the surgeon's decision to refer eligible patients to the medical oncology service for a discussion regarding neoadjuvant therapy.

Overview

The retrospective chart review was conducted on women, newly diagnosed with breast cancer, to compare the rates of neoadjuvant referral during the calendar year of 2013 (pre-guideline dissemination) and in 2016 (post-guideline dissemination). The data were extracted from the provincial cancer registry, three computer systems consisting of the hospital-based system (MediTech), the former DHBMCC system (OPIS), and the new DHBMCC electronic record system (ARIA), as well as the former DHBMCC paper patient charts. Data were extracted from these same sources on patient demographics, as well as tumor- and facility-related characteristics to help identify the factors most likely to influence the surgeons' decision to refer.

Health care professionals, including clinical nurse investigators, have been using the medical records of patients to conduct retrospective research for the purpose of quality assurance and improvement in clinical practice for many years. In fact, researchers have found that retrospective chart reviews comprise about 25% of published scientific research (Vassar & Holzmann, 2013; Worster & Haines, 2004). Retrospective chart reviews allow for a direct chronology of events between exposure and outcomes from which the investigator can determine association (but not causation). Retrospective chart reviews are also beneficial for conducting quality assurance studies, pilot studies, or other research

where it is impractical or unethical to carry out as prospective studies (Worster & Haines, 2004). Since the overall aim of this project was to evaluate the neoadjuvant referral process of an oncology program, this approach appeared to be the most practical methodology of choice.

Methods

Setting and Sample

The setting for this evaluation project was located at the DHBMCC in St. John's, within the Eastern Health Regional healthcare district and the Cancer Care provincial program of NL. The sample population of interest consisted of two distinct groups of women who were newly diagnosed with invasive mammary carcinoma, also known as invasive breast cancer, between January 1, 2013 to December 31, 2013 and January 1, 2016 to December 31, 2016. These two groups of women were those with a pathological diagnosis of locally advanced breast cancer and those with a pathological diagnosis of inflammatory breast cancer.

Study Population Criteria

The Eastern Health BDSG "*Neoadjuvant Treatment of Primary Breast Cancer*" guideline describes locally advanced breast cancer as having a clinically large tumor (> 5cm) and/or significant clinical lymph node disease (at least N2) and defined as having either stage IIB (T3N0 only) or any stage III breast cancers as outlined in the American Joint Committee on Cancer (AJCC) breast cancer staging (Edge et al., 2010). A copy of the AJCC breast cancer staging has been added in Appendix A of this report. The BDSG guideline also describes inflammatory breast cancer has an aggressive disease which is characterized by the rapid development of erythema and edema in the breast. This disease

presents clinically with the classic peau d'orange appearance in the skin of the breast and is usually diagnosed pathologically with a skin biopsy. The exclusion criteria were patient cases that consisted of male patients; in situ disease only; metastatic breast cancer on presentation or on initial staging; any AJCC stage of invasive cancer other than those included in the eligibility criteria; and cases which were ineligible for surgery and/or all other cancer-related treatment (chemotherapy, endocrine therapy, radiation therapy).

Outcomes and Variables of Interest

The main outcome of interest was the number of patients who were referred to medical oncology for neoadjuvant treatment consideration for 2013 and for 2016 in order to determine the referral rate for each respective year. This outcome was categorized as being 'referred' or 'not referred'. Several cases were identified where surgeons consulted with a medical oncologist prior to providing surgical treatment and in all cases the surgeons followed the oncologists' recommendations. These cases were categorized as 'referred' with the acknowledgement of the surgeons' consultation with a medical oncologist. The actual treatment sequence received by each patient was categorized as either 'neoadjuvant' or 'adjuvant' treatment.

The variables of interest in this project were those pertaining to a variety of pre-determined patient, tumor and facility-related factors which may play a role in the surgeons' decision-making. The patient demographics of interest were age at diagnosis, year of diagnosis, and pathologic diagnosis. Pre-existing co-morbidities had also been considered initially to be used as a patient demographic but were excluded because pre-existing conditions such as diabetes, hypertension, or obesity have no effect on whether treatment can be offered or not. The decision to deem patients to be ineligible for

treatment tends to be standard for both surgical and pharmaceutical intervention when these patients have a previous medical history of heart failure, stroke, deep vein thrombosis, renal failure, and general frailty. Osteoporosis can also exclude these patients from the option of aromatase inhibitors. Therefore, cases in which the patient was ineligible for definitive surgery and/or one other treatment offered by the DHBMCC (e.g., chemotherapy or radiation therapy) were excluded from the sample.

The tumor characteristics of interest consisted of:

- clinical tumor size
- tumor histology
- tumor grade
- unilateral versus bilateral disease
- unifocal versus multifocal disease
- presence of multicentric disease
- chest wall/skin involvement
- clinical lymph node status
- clinical or pathological AJCC stage
- molecular subtype, and
- the tissue specimen used to perform hormone receptor testing on.

Initially, tumor palpability had been considered a tumor-related factor of interest. However, this factor was not always reported consistently and accurately in the medical record, and therefore was excluded. Two additional tumor-related factors were added which were found to potentially have an impact on decision-making:

1. Molecular subtyping involves special testing based upon the presence/absence of hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), and the potential over-amplification of the human epidermal growth factor receptor (HER2). The presence of certain molecular subtypes such as HER2 positive (i.e., ER/PR negative, HER2 positive) and triple negative breast cancers (ER/PR/HER2 negative) indicates an important component which may affect the surgeons' decision to refer, if available at the time decision-making takes place; and
2. Whether the testing to garner this information was performed on the needle core biopsy or the post-operative surgical specimen.

The facility-related factor consisted of the name of the facility which, in turn, provided information regarding whether the healthcare facility was a university-affiliated institution or a community hospital.

Diagnostic and Decision-Making Process

Two algorithms were designed by the investigator accompanied by a corresponding description. The 'Diagnosis and Treatment' algorithm and description are provided in Appendix B. Its purpose was to clarify the diagnostic process for patients with breast cancer by featuring the sequence of events after a suspicious lesion has been found. The 'Surgeons' Decision to Refer' algorithm and accompanying description are located in Appendix C. This algorithm outlines the three options that surgeons' can choose from when deciding whether to proceed with surgery, refer the patient for neoadjuvant discussion, or collaborate with a medical oncologist to discuss treatment sequencing.

Data Collection

The data collection process was distinctly different between the study years of 2013 and 2016 due to the variation and number of data sources involved. The 2013 patient cases were available in paper chart format with the addition of DHBMCC physician progress notes in the electronic OPIS computer system. The 2016 dataset was available only on electronic records via the ARIA computer system. The ARIA system required only a user name and password, and minimal training to access the necessary records for abstracting the data. ARIA housed all patient reports from diagnostic imaging, operating room, and pathology as well as the progress notes from oncologists and surgeons, including letters of correspondence between surgeons and family doctors. The 2016 data were extracted from three sources: the cancer registry dataset, the ARIA electronic patient records, and occasionally the hospital MediTech computer system. The 2013 data were extracted from four sources: the cancer registry dataset, the DHBMCC paper charts, the former OPIS and the MediTech computer systems. Each of the data sources will be described below and followed by a table outlining the best source from which the variables of interest could be found.

Cancer Registry Database.

The NL Cancer Registry is a national cancer database which is governed and operated by the Eastern Health Provincial Cancer Care Program. The registry collects cancer-related health information and uses it to monitor and promote the improvement of cancer care within the province. A letter of request was drafted and emailed to the divisional manager of the provincial cancer registry, and a copy of which has been included in Appendix D. It outlined the eligibility criteria and years of interest for this

study. One of the responsibilities of the divisional manager, a registered cancer registrar, is to extract cancer registry data for approved research, evaluation and quality improvement projects. The divisional manager completed the search of the cancer registry database and the resulting list of patients' names, ages, corresponding medical care plan (MCP) numbers, and coded tumor-related data were entered into an Excel spreadsheet. These were emailed to the investigator along with a copy of the decoding information.

OPIS Computer System.

The OPIS computer system was the former system used only at the DHBMCC prior to the 2014 introduction of the ARIA electronic record. The OPIS system was used as a method for tracking patient charts and clinic appointments, in addition to recording the patients' personal identification information and the dictated oncologists' first assessment and progress notes. However, no hospital, laboratory data, or outside communication between physicians was available on this system.

It was extremely difficult to obtain access to the defunct OPIS computer system from the Heath Technology and Data Management (HTDM) department, despite a formal request from the Program Director and multiple email correspondence between the HTDM and the investigator. Finally, it was determined that access was only available through the office computers of a small number of oncologists who practiced at the DHBMCC before 2014. This method of access was not a practical approach for the number of cases that needed to be researched, the amount of time required, and the interference with the oncologists' regular office work schedule. The decision was made to perform a hand search of the available paper charts to obtain the majority of the data required, leaving the OPIS system for access to the health information of patients

(consisting of only two) whose paper charts had been stored in an external storage facility. These reviews, and any additional data not available from paper charts, were conducted on an OPIS-equipped computer of an oncologist colleague, who allowed the investigator the opportunity to access the system while the oncologist attended clinic patients.

The OPIS system was also useful in eliminating 16 patients on the cancer registry dataset who had never been seen within the Cancer Care Program. There are a variety of reasons why patients who were referred to the program would have never been seen by an oncologist including the patient's choice to refuse the consult, the patient being considered too unwell, or the death of the patient prior to appointment from the effects of cancer or other health issues.

Paper Patient Charts.

The majority of the paper charts of patient cases diagnosed in 2013 were located in the Medical Records department of the DHBMCC and the manager of the Medical Records division gave the investigator permission to access the paper charts included in the study. The data collection required a special identification number derived from a portion of the patient's MCP number. The investigator was instructed by the medical records staff on the three areas within the Medical Records department where the paper charts were filed, as well as description of how to determine the 'look-up number' for locating specific charts. The manager informed the investigator, at that time, that due to the limitation of space within the department, some old paper charts had been removed and stored in an outside facility. However, the manager of Medical Records felt confident

that since the year of interest was just one year prior to the ARIA electronic record system coming online, most of the charts should be still at the DHMBCC, later found to be true.

Since the cancer registry dataset provided the patients' MCP numbers, the investigator determined the look-up number and located all but two of the paper charts successfully. The investigator selected two to three charts at a time from the list provided by the tumor registry dataset and collected the data using a data collection tool for each case. All imaging, operating room and pathology reports outside the Eastern Health region were located on the paper charts. This was a common practice employed by the clerical staff as part of their duties to ensure all patient-related information was available to the oncologist when seeing a new patient at the DHBMCC for the first time. Once requested, this information would be faxed to the DHBMCC from any hospital in the province since no computer access to other health authorities existed at that time. Occasionally, the investigator would find that similar type of reports from within the Eastern Health district were not available on the paper chart, however the data was easily accessible through the hospital MediTech system.

Though time consuming, the paper patient chart was the best source of data for cases diagnosed in 2013. The investigator was intimately aware of the paper chart used at the DHBMCC, having worked as the Primary Nurse for the Medical Oncology clinics for ten years. This enabled the investigator to quickly and efficiently locate the data and interpret the sequence of events.

MediTech Computer System.

Though not necessary for use in all patient cases, the Meditech system was useful on occasion for obtaining data from within the Eastern Health district for cases diagnosed

in both 2013 and 2016. This was especially true for those cases where the paper chart, or occasionally, the electronic record was missing some specific data from imaging, pathology reports or written communication between the surgeon and the family physician.

ARIA Computer System.

The ARIA system was the single most important data source for patients diagnosed in 2016. The majority of information on imaging, operating room reports, pathology, surgeon progress notes, oncology first assessment and progress notes (both radiation and medical oncology) were easily accessible. The system was highly convenient since it was available on any work computer at the DHBMCC and the center offered the services of an ARIA nursing support person to aid in navigating the ARIA system, if needed.

The ARIA system was also useful for helping to determine whether the staging investigations ordered by surgeons revealed the presence of metastatic disease for patient cases from both 2013 and 2016. The investigator was also able to track incidental findings on some staging investigations which later was confirmed through re-imaging to be early evidence of metastatic disease. The ARIA system was also helpful in determining whether referred patients were physically suitable for definitive surgery and/or other treatment modalities when surgical notes were lacking. In both cases, the information provided helped exclude patient cases that did not conform to the eligibility criteria. As already indicated, there are many data sources in this project as well as a large number of variables of interest. Table 1 provides a summary of the best source to access in order to extract the necessary data for a particular variable according to the study year.

Table 1

Sources for Data Collection

Variable	**Pre-Implementation (2013)**				**Post-Implementation (2016)**		
	Cancer Registry	**Paper Chart**	**OPIS**	**Medi-Tech**	**Cancer Registry**	**ARIA**	**Medi-Tech**
Patient age	X				X		
Year of diagnosis	X				X		
Clinical tumor (T) size	X				X		
Tumor histology		X	X	X		X	X
Tumor grade		X	X	X		X	X
Unilateral/ bilateral		X	X	X		X	X
Multifocal/ multicentric		X	X	X		X	X
Clinical nodal status (N)		X	X	X		X	X
Clinical/ pathological AJCC stage	X				X		
Estrogen/ progesterone receptor status	X				X		
HER2 receptor status	X				X		
Chest wall/skin involvement	X				X		
Facility location		X	X	X		X	X

Data Collection Tool.

To extract the data in an organized and efficient manner, a paper data collection tool was required which in turn warranted the need for a data dictionary. The data dictionary defined the specific data to be collected and ensured that all

data was accurately coded from the medical record. The purpose of these tools was to allow ease of data entry, maintain data accuracy, and to standardize the process. However, developing a new data collection tool could be a time-consuming and an unnecessary step, especially when many excellent tools are available online which can be modified for personal use. Nurse researchers, Gregory and Radovinsky (2012) have provided an excellent example of a data collection form, as well as a data dictionary, which the investigator adapted for use in this project. A copy of the adapted data collection form and data dictionary are located in Appendix E and F. These authors emphasized the need for appropriate organization or grouping of the variables in order to efficiently extract the data as it appears in the medical record. Therefore, all variables were grouped in the data collection tool to allow efficient extraction of the data from the same locations in the chart.

Data Management

The investigator chose to create separate Excel spreadsheets by study year in which to house the extracted data, labeled as evaluation data and according to year. Each spreadsheet was constructed with suitable headings which reflected the variables of interest for this project. Along with the coded cancer registry dataset, the divisional manager of the tumor registry also provided the investigator with a copy of the explanation of what each of the codes represented. The coded data was used to describe

tumor size, lymph node status, and how to evaluate lymph node involvement of each patient case. A copy of these coding explanations has been included in Appendix G. Using the information obtained from the coded cancer registry database, the data were then transferred into the Evaluation Data Excel spreadsheets as indicated by study year, under the appropriate headings.

The next step in the process was to extract the remaining data through a chart review. The ideal method for entering the data extracted from the various data sources would have been with the aid of a laptop computer assigned solely to the investigator, allowing the data to be entered directly into the Evaluation Data Excel spreadsheets. However, due to the financial constraints, it was difficult for the management of the Cancer Care Program to provide a laptop computer for each staff member. There are two laptops available to all staff within the program when needed. However, this raises concerns for the investigator on the ability to protect the privacy of patient information being collected. Therefore, the decision was made to develop an appropriate paper data collection tool to capture the required extracted data from the various sources.

Statistical Analysis.

The statistical analysis of these data was conducted using the Microsoft Excel 365 software for Windows 10. Confidence intervals (CI) were calculated for the overall referral rates and the T3/T4 tumor only referral rates for both 2013 and 2016, using a 95% CI. It had been the intention of this investigator to perform a multivariable analysis on the data obtained, however the resulting sample size was too small to allow for such an analysis.

Pilot Test.

The investigator chose the first fifteen patient cases in the 2016 dataset to pilot test the data collection tool. The results were instrumental in providing insight into the lack of consistent data required for two of the chosen variables of interest. As previously mentioned, the palpability of the tumor and the patients' pre-existing co-morbidities may well be important variables in the surgeons' decision-making. However, the lack of consistent surgeon reporting of clinical visits created a gap in the data collected and led to the exclusion of these two variables. In addition, the pilot test demonstrated the lack of synoptic pathology reporting for some hospitals in the province which made it difficult on occasion, to accurately record data on the tumor focality variable of interest.

The pilot test also helped the investigator realize the necessity for adding certain variables, such as the molecular subtype of the tumor and which specimen it was tested on, which would likely be of use for surgeons during decision-making. Recent evidence revealed that triple negative and HER2 positive breast cancer subtypes treated with neoadjuvant therapy confer a survival advantage for patients (Broglio et al., 2016; Houssami, Macaskill, von Minckwitz, Marinovich, & Mamounas, 2012). This would likely be a motivating factor for surgeons and oncologists alike, to pursue the use of neoadjuvant therapy in this cohort.

It became apparent during the pilot test that some surgeons had contacted a medical oncologist prior to commencing surgery to discuss the case and decide a course of action. In each case encountered, the surgeon acted on the advice of the oncologist and the investigator felt that this should be acknowledged as a referral, despite the oncologist never having seen the patient face-to-face. Therefore, two additional headings were added

to the data Excel spreadsheets which included whether cases were either referred/not referred for neoadjuvant therapy and the final choice of treatment sequence (neoadjuvant or adjuvant). The utilization of a pilot test was extremely helpful in streamlining the quality of the data being extracted from the chart review.

Promoting Data Quality

Retrospective chart reviews are also associated with some commonly identified shortcomings such as "…incomplete or missing data within the medical record, records lacking specific patient information, difficulty in interpreting or verifying documented information, and variability in the quality of documentation among health care personnel" (Gregory & Radovinsky, 2012, p.109). These limitations can result in the introduction of systematic error and interpreter bias which can skew the outcomes and negatively affect the internal validity of the study (Kaji, Schriger, & Green, 2014). The investigator of this study also experienced incidents where certain variable data were missing (e.g., lack of reporting of pathological tumor focality) and had to be reported as unknown; or the variability (or lack thereof) of surgeons' documentation prevented the extraction of a complete dataset resulting in the omission of the variable in question. Though a substantial improvement in documentation was noted from that of 2013 compared to 2016, the problem persisted in 2016 with variation among hospitals and surgeons.

The investigator took measures to help mitigate some of the limitations within control by improving the transparency and rigor of the process. Having an experienced certified cancer registrar carry out the search for potentially eligible patient cases from the provincial tumor registry was an important measure in which to establish the rigor of a study. A chart review was still necessary however, to aid in identifying patient cases which did not meet

the eligibility criteria and to extract the required data from both paper charts and electronic computer records, not available from the tumor registry database. As a primary nurse with several years of clinical experience working within the medical oncology discipline, the investigator and sole data collector had the expertise necessary to conduct the chart review while minimizing data collection error.

The utilization of a well-developed data collection tool accompanied by a detailed data dictionary have been attributed to an increase in the interrater reliability of the chart review data collection process (Gregory & Radovinsky, 2012). Interrater reliability is basically the degree of agreement among how several data extractors collect data in a similar fashion. As this study has only one data extractor, it could be argued that the intra-rater reliability was high however, a single data extractor can also introduce selection bias. Therefore, it was fundamentally important for the data collection process to remain consistent throughout to aid in reducing systematic error and investigator bias during the data collection process.

Controlling all confounding factors is an impossible task during a study, however it is necessary to control those which can be controlled. Pre-existing co-morbidities are difficult to measure, and the lack of consistent surgical clinical documentation prevented its use as a variable of interest in this evaluation study. Nevertheless, the presence of co-morbidities in the sample population could be expected to have a significant confounding effect on the results of this study. Occasionally, in the investigators' experience, patients with pre-existing co-morbidities are referred to medical oncology by surgeons who are reluctant to perform surgery but still want to be able to offer these patients some form of treatment. Therefore, measures were taken to ensure that the inclusion criteria allowed only those

cases who were able to undergo definitive surgery and at least one other treatment option offered in the cancer care program (e.g., endocrine therapy, chemotherapy or radiation therapy).

Ethical Considerations

Permission was granted from the program director of the provincial cancer care program to conduct this evaluation project and provided access to the provincial cancer registry and the various computerized electronic patient health records. The permission was granted on the basis that this evaluation study met the standards of the Newfoundland and Labrador's Health Research Ethics Authority (HREA). The HREA has the responsibility for reviewing any research proposal which involves conducting research on living human participants. However, according to its website some studies are exempt from HREA approval such as "…quality assurance and quality improvement studies, program evaluation activities, performance reviews, and testing within normal educational requirements if there is no research question involved (used exclusively for assessment, management or improvement purposes)" (HREA website, bullet #3). A tool developed by the Alberta Research Ethics Community Consensus Initiative and provided on the HREA website was helpful in determining whether a study can be classified as research or a quality assurance initiative. It consists of a series of questions regarding the study and provided a numerical interpretation of the study's intention, the results of which indicate that this evaluation project is a program evaluation activity and is exempt from HREA approval. A copy of the completed tool for this evaluation project has been added to Appendix H of this report.

The investigator took several measures to ensure the privacy and protection of the health information of patient cases in this evaluation study. The original tumor registry datasets have been kept on an encrypted USB flash drive and kept in a locked drawer within the investigator's locked office at the DHBMCC. It will remain so for a period of five years until which time the data will be destroyed. The data of interest was collected from the tumor registry datasets and entered on separate data Excel spreadsheets designed by the investigator which included the patient case identifiers such as names and corresponding MCP numbers. Once the investigator collected the remaining data of interest from the chart review and completed the data entry into the newly constructed spreadsheet, the process of data de-identification was initiated. This process required the removal of all patient names and MCP numbers with each case being assigned a replacement unrelated number, which protected the anonymity of the patients and their personal health information. The new Excel spreadsheets with the de-identified data are being kept on a password protected work computer in the locked office of the investigator in a security-controlled work environment at the DHBMCC.

Results

A closer examination of the original tumor registry datasets revealed that many of the cases did not meet the eligibility criteria. In the 2013 dataset, the total number of patient cases in the sample was 113. However, 64 cases were excluded due to ineligibility leaving a total of 49 patient cases for 2013. In the 2016 dataset, the total number of patient cases in the sample was 133 with 77 cases excluded resulting in a total of 56 patient cases.

Furthermore, during the data collection process, it became obvious that some patients were referred mainly because their pre-existing co-morbidities prevented primary surgery due to an elevated risk of death. This left the surgeon with little recourse other than to refer in hopes that a medical oncologist could offer some less risky means of treatment, which is rarely the case. At this juncture, in an attempt to create a more homogeneous sample population, the decision was made to only include patient cases who were candidates for at least two of the three main treatment options for breast cancer (i.e., surgery, pharmaceutical or chemical intervention, radiation therapy). Those cases that did not meet this stipulation were excluded and resulted in two additional patient cases being excluded for each study year from the locally advanced breast cancer sample population.

The Figure 1 flowchart was designed in order to provide clarification of the sample population by year, by diagnosis, and finally whether cases were referred, not referred or not candidates for treatment. In 2013, of the 45 patient cases with locally advanced breast cancer only 10 were referred for neoadjuvant consideration, while 33 were not and two were ineligible. The four patient cases having inflammatory breast cancer in 2013 were all eligible and referred for neoadjuvant treatment. The final sample size for 2013 was 47 patient cases.

In 2016, of the 56 patient cases with locally advanced breast cancer only 14 were referred, 38 were not, and two were ineligible. The two cases with inflammatory breast cancer in 2016 were eligible and both were referred for neoadjuvant consideration. In 2016, the final sample size was 54 patient cases.

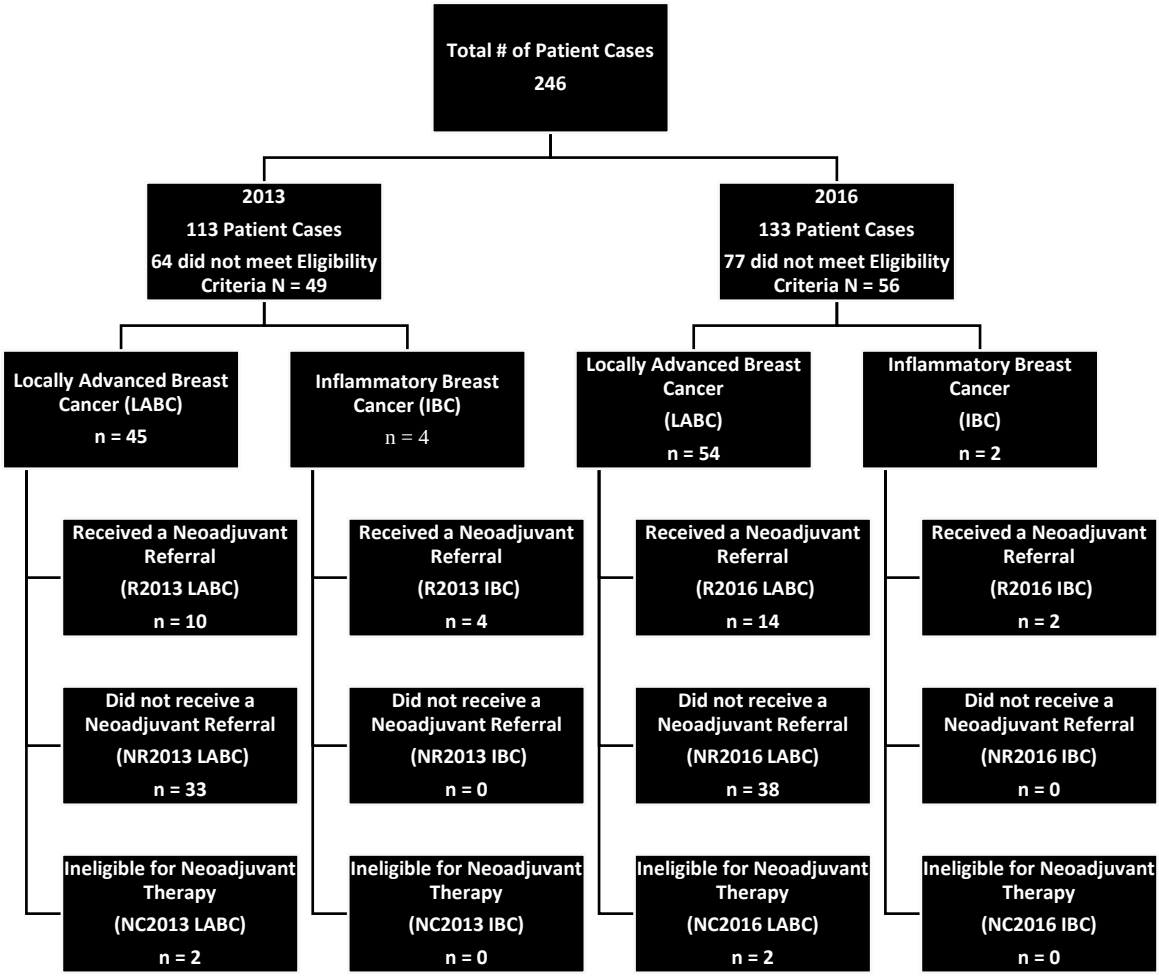

Figure 1. Evaluation Project Study Groups Flowchart.

Inflammatory Breast Cancer

There were four cases of inflammatory breast cancer in 2013 and only two cases in 2016. All six cases were referred for neoadjuvant consideration by the surgeons in question, which is 100% of patient cases for both years. This rate exceeds the range found in the literature review of 72% to 93% for neoadjuvant guideline adherence for the study

population with a diagnosis of inflammatory breast cancer. While the numbers were small, the referral rates for inflammatory breast cancer did indicate 100% compliance at least for the two years studied therefore, the remaining analysis will focus solely on the locally advanced breast cancer cohort only.

Locally Advanced Breast Cancer

Table 2 summarizes the comparison between the number and proportion of cases that were referred and not referred according to the study year of the locally advanced breast cancer cohort. A detailed discussion of the results has been provided below under the appropriate diagnostic heading. As shown in Table 2, the referral rates for those diagnosed with locally advanced breast cancer revealed a considerably different picture than that of the inflammatory breast cancer cohort. The analyses for 2016 suggests that only approximately 27% with a 95% CI [14.9%, 39.0%], of the eligible sample population of locally advanced breast cancer cases were referred to the medical oncology discipline. Using a confidence interval (CI) indicates that the likelihood of the true referral rate can be expected to be as low as 14.9% or as high as 39% for the 2016 results. The results for 2013 were similar with a referral rate of 23% having a 95% CI [10.6%, 35.9%]. In this case, the likelihood is that the true referral rate could be as low as 10.6% or as high as 35.9%. Regardless, both referral rates for 2013 and the 2016 were much lower than the range of 44% to 79% adherence to neoadjuvant guidelines identified in the literature review. It was also clear that there was considerable overlap of the CI ranges for both years which indicates that there were little or no difference between the referral rates. A closer look at the data for all patient cases with locally advanced breast cancer

was warranted to determine if any of the identified variables may have influenced these results.

Table 2

Number and Proportion of Patients Diagnosed with Locally Advanced Breast Cancer (LABC) in 2013 and 2016

	2013 N = 43		**Total n (%)**	**2016 N = 52**		**Total n (%)**
	Referred n (%)	**Not Referred n (%)**		**Referred n (%)**	**Not Referred n (%)**	
Locally Advanced Breast Cancer (LABC)	10 (23.3%)	33 (76.7%)	43 (100%)	14 (26.9%)	38 (73.1%)	52 (100%)

Patient Demographic and Facility Variables for LABC.

Table 3 summarizes the results of this cohort by the patient demographic of age and facility-related data according to the referral status and study year. The facility data gave information regarding the name of the facility which in turn, informed the investigator whether the definitive surgery had been performed in a large university-affiliated hospital versus moderate to small urban hospitals or a small rural community hospital. All of the numbers were too small or too similar in this table to reliably be able to draw conclusions. However, there were some instances where the investigator was able to identify some notable trends in the data.

Table 3

Patient Age and Facility Type of LABC by Year and Referral Status

Variables	**2013**		**2016**	
	Referred n (%)	**Not Referred n (%)**	**Referred n (%)**	**Not Referred n (%)**
Age Range (years)	**Median Age: 58 Range: 35 to 85**		**Median Age: 61.5 Range: 33 to 85**	
≤ 40	3 (100)	0(0)	1(33.3)	2(66.7)
41 – 50	2(22.2)	7(77.8)	5(55.6)	4(44.4)
51 – 60	2(20)	8(80)	4(33.3)	8(66.7)
61 – 70	3(37.5)	5(62.5)	2(11.1)	16(88.9)
> 70	0(0)	13(100)	2(20.0)	8(80.0)
Facility Type				
Large Urban (University-affiliated)	8(40.0%)	12(60.0%)	8(24.2%)	25(75.8%)
Moderate Urban Community Hospital	1(11.1%)	8(88.9%)	2(33.3%)	4(66.7%)
Small Urban Community Hospital A	0(0)	8(100)	0(0)	3(100)
Small Urban Community Hospital B	0(0)	1(100)	3(60.0)	2(40.0)
Other (Small Rural Community Hospitals)	1(20.0%)	4(80.0%)	1(20.0)	4(80.0)

The median age and range for 2013 and 2016 was 58.0 years (35 years to 85 years) and 61.5 years (33 years to 85 years), respectively. One of the data trends was related to the stratified age groups which indicated a higher proportion of cases aged 41 to 50 years were being referred in 2016 (55.6%) compared to the same age group in 2013 (22.2%). Interestingly, another trend that was identified in the data was a larger number of cases in the 61 to 70-year age group for 2016 compared to 2013 (18 cases vs. 8 cases), however a smaller proportion of them had been referred in 2016 (11.1% vs. 37.5%). The most important exception of note was regarding the facility-related data which indicated that despite having a larger number of patient cases receiving definitive surgery at university-affiliated hospitals in 2016 (33) compared to 2013 (20), the proportion of cases being referred were lower in 2016 (24.2%) compared to 2013 (40%).

Tumor Size, Lymph Node Status, and AJCC Staging for LABC.

Table 4 summarizes the locally advanced breast cancer data by tumor size, nodal status, and AJCC staging according to referral status and the year of study. The 2013 results indicated that larger tumor sizes (> T2) were more likely to be referred (67%; six out of nine) than those ≤ T2 (13%; four out of 30) (see Appendix A for explanation of T sizes). This was also the case with the 2016 results which showed that 11 out of 18 (61%) cases with tumors > T2 were referred while only three out of 34 (9%) cases of tumors ≤ T2 were referred. This also held true for those with lymph node involvement, who were much more likely to be referred compared to those with negative lymph nodes. In 2013 nine cases with lymph node involvement were referred compared to one with no lymph node involvement. In 2016, 14 cases with lymph node involvement were referred while there were no cases of lymph node negative disease referred. There was also a data trend

suggesting that there were a larger number of stage IIIA breast cancers (32) in 2016 compared to 2013 (26), with a slightly higher proportion of these having been referred for neoadjuvant therapy in 2016 (31% vs. 23%).

Table 4

Tumor Size, Lymph Node Status, and AJCC Stage of LABC by Year and Referral Status

Variables	2013		2016	
	Referred n (%)	Not Referred n (%)	Referred n (%)	Not Referred n (%)
Clinical Tumor Size*				
Tx	0(0)	4(100)	0(0)	4(100)
T1b	0(0)	3(100)	0(0)	2(100)
T1c	0(0)	8(100)	1(10.0)	9(90.0%)
T2	4(21.1)	15(79.0)	2(11.1)	16(88.9)
T3	5(62.5)	3(37.5)	9(60.0)	6(40.0)
T4	1(100)	0(0)	2(66.7)	1(33.3)
Lymph Node Status				
Negative	1(7.1)	13(92.9)	0(0)	4(100)
Positive	9(31.0)	20(69.0)	14(29.2)	34(70.8)
AJCC Stage (Clin/Path)				
Stage IIB (T3N0M0)	1(25.0)	3(75.0)	0(0)	4(100)
Stage IIIA	6(23.1)	20(76.9)	10(31.3)	22(68.8)
Stage IIIB	1(100)	0(0)	0(0)	2(100)
Stage IIIC	2(16.7)	10(83.3)	4(28.6)	10(71.4)

Other Tumor-related Variables for LABC.

Table 5 summarizes the analysis of the other tumor-related variables such as tumor histology, grade, focality, unilateral versus bilateral, and the molecular subtype of the disease by referral status and year of study. Ductal tumors are the most common histology type found in breast cancer. Therefore, it is not surprising that the majority of the patient cases in this cohort had been diagnosed with ductal histology for both study years. Though the sample size for ductal histology was the same for both years with 28 cases, there was a slight increase in the proportion of cases in 2016 (32%) compared to 2013 (25%). In both 2013 and 2016, the referral rate for grade 3 tumors were virtually the same even though these poorly differentiated tumors are highly aggressive. However, there was a slight trend toward more referrals for grade 2 tumors in 2016 (27.8%) compared to 2013 (21.7%). Grade 2 and 3 tumors were far more likely to be referred in either year compared to those with grade I disease (0%).

Table 5

Other Tumor-related Variables of LABC by Year and Referral Status

Variables	**2013**		**2016**	
	Referred n (%)	**Not Referred n (%)**	**Referred n (%)**	**Not Referred n (%)**
Tumor Histology				
Ductal	7(25.0)	21(75.0)	9(32.1)	19(67.9)
Lobular	0(0)	2(100)	0(0)	4(100)
Mixed	2(22.2)	7(77.8)	4(25.0)	12(75.0)
Other	1(25.0)	3(75.0)	1(25.0)	3(75.0)

Variables	2013		2016	
Tumor Grade				
Grade 1	0(0)	3(100)	0(0)	0(0)
Grade 2	5(21.7)	18(78.3)	5(27.8)	13(72.2)
Grade 3	3(21.4)	11(78.6)	7(22.6)	24(77.4)
Unknown	2(66.7)	1(33.3)	2(66.7)	1(33.3)
Tumor Focality				
Unifocal	2(9.1)	20(90.9)	11(27.5)	29(72.5)
Multifocal	4(44.4)	5(55.6)	3(33.3)	6(66.7)
Multifocal/ Multicentric	0(0)	0(0)	0(0)	1(100)
Unknown	4(33.3)	8(66.7)	0(0)	2(100)
Laterality				
Unilateral	9(22.5)	31(77.5)	12(24.0)	38(76.0)
Bilateral	1(33.3)	2(66.7)	2(100)	0(0)
Molecular Subtype				
Luminal A/B	6(20.0)	24(80.0)	7(19.4)	29(80.6)
HER2 Positive	0(0)	1(100)	0(0)	3(100)
Triple Negative	4(33.3)	8(66.7)	7(53.8)	6(46.2)

Unifocal tumors are much more commonly found in the breast cancer population than multifocal tumors or multifocal/multicentic disease. However, unifocal tumors are also far less aggressive than multifocal tumors or those with multifocal/multicentic

disease. The numbers were really too small and too similar to determine whether multifocality or multifocal/multicentric disease were truly a characteristic of influence for both years of study. A larger sample size may be able to answer this question more conclusively.

Similar to the trends found for ductal histology and unifocal tumors, the findings of unilateral disease are also far more common than that of bilateral disease in breast cancer. In addition, the presence of bilateral tumors indicates a far more advanced and aggressive pathology than that of unilateral disease. The numbers for bilateral disease were too small to identify a trend.

The referral rates for luminal (approximately 19% to 20%) and HER2 positive (0%) breast cancers were similar for both study years. However, there was one noteworthy trend in the data which concerned the difference in referral rates of the triple negative molecular subtype. Despite the small numbers, it was evident that a higher proportion of triple negative cases were referred in 2016 (53.8%; seven out of 13) compared to 2013 (33.3%; four out of 12).

Argument for Subgroup Analysis

The only findings in the results which appear to provide an explanation for such a low referral rate for all locally advanced breast cancers would be the tumor size and presence of lymph node involvement. This coincides with one of the three characteristics used to define the locally advanced breast cancer population which were:

- a tumor size > 5cm (T3 or T4); and/or

- at least N2 disease defined by the AJCC staging manual on breast cancer staging as "…clinically fixed/matted ipsilateral axillary lymph nodes or clinically imaged ipsilateral internal mammary nodes in absence of clinically evident axillary lymph node…" involvement (Edge et al., 2010, p.2); and/or
- AJCC stages IIB (T3N0M0) or any stage III breast cancer.

The clinical assessment of the T size is frequently easily determined by measurement under clinical palpation or radiological measurement under imaging with a T size assigned according to the measurement (in mm). An exception to this would be tumors classified as Tx which indicates that clinical disease can be detected in the axillary lymph nodes however, there is no evidence of tumor clinically or radiologically detected in the breast. The clinical T3 or T4 tumors in any sample would unequivocally meet the definition of locally advanced breast cancer and routinely should have been referred for neoadjuvant treatment.

In the presence of smaller tumor sizes, such as T1 and T2 (either clinically or radiologically), a clinical diagnosis of N2 disease is required to confirm a locally advanced breast cancer diagnosis requiring a neoadjuvant referral. However, in this case the clinical assessment of the axillary lymph nodes to detect N2 disease can be much more challenging even with the aid of radiological imaging. The axillary contents are much denser than the breast and often requires the use of ultrasound to help detect enlarged lymph nodes. 'Pathological' lymph nodes are lymph nodes detected during imaging measuring at least 1cm or larger which are suspicious for the presence of a disease process. Lymph nodes smaller than 1 cm can sometimes be visualized on imaging

by the radiologist but often cannot be categorically defined as pathological. Unless there are at least two levels of ipsilateral pathological axillary lymph nodes, or ipsilateral pathological internal mammary node involvement visualized on imaging, then the N status cannot be classified as N2 disease. Therefore, these cases would not be eligible for neoadjuvant therapy when combined with a T size of 2 or smaller.

In some cases where imaging suggests N1 or no nodal disease, the aggressiveness of some breast cancers may create regional lymph nodes involvement with tumor at a N2 level, without these lymph node(s) reaching pathological size at the time of imaging. In these cases, the extent of disease will only be revealed during the pathological analysis after definitive surgery which is too late to take advantage of the benefits of neoadjuvant therapy. Therefore, without the aid of a clear indication of N2 disease and in the presence of a T2 or smaller tumor size, the surgeon will correctly proceed with definitive surgery.

There were a group of patient cases within this cohort which, according to the definition of locally advanced breast cancer, should have been referred without question. The use of AJCC staging would not be helpful in identifying this group since it too would require detailed clinical knowledge of the nodal status. However, breast cancers having clear evidence of T3 and T4 tumors should automatically be candidates for neoadjuvant therapy and therefore, should be a suitable cohort in which to investigate a more accurate representation of the actual referral rate. Therefore, the remaining analysis will focus on the locally advanced breast cancers with T3 and T4 tumors.

Locally Advanced Breast Cancer (T3/T4 only)

A comparative analysis was performed on T3 and T4 locally advanced breast cancers according to the study year, and the results are outlined in Table 6. The number of

T3 and T4 cases doubled in number for 2016 (n = 18) compared to 2013 (n = 9). However, the referral rate decreased from approximately 67% (95% CI: 35.9%, 97.5%) in 2013, to approximately 61% (95% CI: 38.6%, 83.6%) in 2016. In 2013, the likelihood of the true referral rate can be expected to be as low as 35.9% or as high as 97.5%, while the true referral rate for 2016 would be between 38.6% and 83.6%. The confidence intervals in both study years are notably wide. Taking into consideration the sample sizes were small, the referral rates for both study years do fall within the range identified in the literature review of 44% to 79%. However, a larger sample size would allow for a more accurate estimate of the referral rate with a narrower confidence interval, and a clearer picture of the true rate.

Nevertheless, in 2016 nearly 40% of patient cases with clear evidence of locally advanced disease were not referred for neoadjuvant therapy. The question then became 'was there an association between the chosen variables of interest and the referral status of patient cases with T3 and T4 breast cancer in 2016?'

Table 6

Number and Proportion of Patients Diagnosed with T3 and T4 Locally Advanced Breast Cancer (LABC) in 2013 and 2016

T size of Breast Cancer	**2013 (T3 & T4) n = 43**		**Total n (%)**	**2016 (T3 & T4) n = 52**		**Total n (%)**
	Referred n (%)	**Not Referred n (%)**		**Referred n (%)**	**Not Referred n (%)**	
T3	5(55.6%)	3(33.3%)	9 (20.9%)	9(50.0%)	6(33.3%)	18 (34.6%)
T4	1(11.1%)	0(0)		2(11.1%)	1(5.6%)	
Total	6(66.7%)	3(33.3%)	n = 43 (100%)	11(61.1%)	7(38.9%)	n = 52 (100%)

Patient Demographic and Facility Variables (T3/T4).

The analysis of the T3 and T4 data for 2016 was summarized in Table 7 according to the patient demographic of age and facility type based on whether the patient cases had been referred or not. As previously was the case, the numbers are small which hinders the ability to draw any meaningful conclusions. The median age of the referred group was 54 years with a range of 34 to 79 years of age, while the median age for the non-referred group was 55 years with a range of 33 to 85 years of age. Of the seven cases that were ≤ 50 years of age, five were referred for neoadjuvant therapy while six of the 11 cases that were > than age 50 were referred which may indicate that younger patients are more likely to be referred than older patients. The facility-related data suggests that patient cases in the T3/T4 cohort, who received their definitive surgery at university-affiliated hospital, were more likely to be referred (six of the nine cases) compared to other facilities (five of the remaining nine cases) in the province.

Table 7

Patient Age and Facility Type of Clinical T3 and T4 Tumors of LABC by Referral Status for 2016

Variables	**Referred n = 11**	**Not Referred n = 7**
Age Range (in years)	**Median Age: 54 Range: 34 to 79**	**Median Age: 55 Range: 33 to 85**
≤ 40	1	1
41 – 50	4	1
51 – 60	3	2
61 – 70	2	2
> 70	1	1

Variables	Referred n = 11	Not Referred n = 7
Facility Type		
Large Urban (University-affiliated)	6	3
Moderate Urban Community Hospital	1	2
Small Urban Community Hospital B	3	2
Other (Small Rural Community Hospitals)	1	0

Lymph Node Status and AJCC Stage (T3/T4).

The analysis of the lymph node status and AJCC stage in the T3 and T4 cohort has been provided in Table 8 by referral status. It was apparent from these data that those T3/T4 cases with lymph node involvement were more likely to be referred (11 of 18 cases) than those who did not (0 of 2 cases). In addition, the AJCC stages of IIIA (seven of 11 cases referred) and IIIC (all four cases referred) indicated that these stages were more likely to be referred than stages IIB and IIIB with 0 cases referred.

Table 8

Lymph Node Status and AJCC Staging of Clinical T3 and T4 Tumors of LABC by Referral Status for 2016

Variables	Referred n = 11	Not Referred n = 7
Lymph Node Status		
Negative	0	2
Positive	11	5

Variables	Referred n = 11	Not Referred n = 7
AJCC Stage (Clinical or Pathological)		
Stage IIB (T3N0M0)	0	2
Stage IIIA	7	4
Stage IIIB	0	1
Stage IIIC	4	0

Other Tumor-related Variables (T3/T4).

Table 9 summarizes the analysis of the data from the 2016 study year of the other tumor-related variables for T3 and T4 tumors according to referral status. As mentioned previously, tumors with a ductal histology (8 out of 18), grades 2 or 3 (9 out of 18), a unifocal (9 out of 18) and/or unilateral distribution (9 out of 18) are not only the most common features but also among those most likely to be referred. Five of 11 cases with the luminal subtype were referred while six of the seven cases triple negative subtype were referred. This indicates that those with a triple negative subtype was more likely to be referred than any other subtype.

Table 9

Other Tumor-related Variables of Clinical T3 and T4 Tumors of LABC by Referral Status for 2016

Variables	Referred n = 11	Not Referred n = 7
Tumor Histology		
Ductal	8	1
Lobular	0	2
Mixed	2	3
Other	1	1
Tumor Grade		
Grade 2	4	4
Grade 3	5	3
Unknown	2	0
Tumor Focality		
Unifocal	9	5
Multifocal	2	1
Unknown	0	1
Tumor Laterality		
Unilateral	9	7
Bilateral	2	0
Molecular Subtype		
Luminal A/B	5	6
HER2 Positive	0	0
Triple Negative	6	1

Discussion

Referral Rates and Adherence.

The results of the analyses indicate that the neoadjuvant referral rate for the six patient cases with inflammatory breast cancer in 2013 and 2016 was 100%. This suggests that there has been complete compliance to the recommendations for treatment of inflammatory breast cancer for these patients during both years of study.

However, the interpretation of the data regarding the referral rate for the locally advanced breast cancer sample appears to be much more complex. The initial results suggested that only approximately 27% (95% CI:14.9%, 39.0%) for all-comers in 2016 who met the definition of locally advanced breast cancers on clinical assessment or final pathology were referred to medical oncology for neoadjuvant consideration. This result was only incrementally larger than the 2013 rate of approximately 23% (95% CI: 10.6%, 35.9%). The observed referral rates for 2013 and 2016 were much lower than the referral rate identified in the literature of 44% to 79%.

The subgroup analyses conducted on the T3 and T4 tumors was justified since these patient cases conclusively met the definition of locally advanced breast cancer. These breast cancer cases were among the few where the surgeon was aware that these were locally advanced prior to making the decision to refer the patient or not. This was reflected in a substantial increase in the referral rates for this subset of approximately 67% (95% CI: 35.9%, 97.5%) in 2013 and 61% (95% CI: 38.6%, 83.6%) in 2016. These rates did fall within the literature identified range of 44% to 79%. However, both referral rates have very wide confidence intervals which make it difficult to estimate the true referral rate and can only be narrowed by using a larger sample size. Nevertheless, the

most alarming result in 2016 was that approximately 40% of the patients with T3 or T4 locally advanced breast cancer, who should have received a referral to medical oncology for a neoadjuvant discussion, did not.

Another important insight of this study has been the relatively incremental differences between 2013 and 2016, in terms of guideline adherence in both analyses. Therefore, it is reasonable to state that the study results reveal that there has been little or no difference in the referral rate between study years. This would also indicate that the dissemination of the Eastern Health BDSG neoadjuvant guideline has had little or no effect on the clinical practice of referring eligible cases for neoadjuvant treatment. Unfortunately, this result is hardly surprising since lack of adherence to clinical practice guidelines has been a consistent problem in Canada, as well as many other developed countries, as outlined in the literature (Gupta et al., 2016; Hall, Irish, Gregg, Groome, & Rohland, 2015). An article in the Canadian Medical Association Journal recognized time and resource availability among the main limitations physicians cite for the lack of use of clinical practice guidelines (Vogel, 2011). Other criticisms of guidelines include their length, complexity, and the variety of choice available from numerous sources. These legitimate complaints must be taken seriously, and measures taken to enhance the usability of the clinical practice guidelines if patient outcomes are to be constructively improved.

Factors and Decision-making.

As was the case for the referral rate analysis, the sample size was too small to allow firm conclusions to be drawn though the identification of trends in the data was still possible. Several trends in the data were identified from the analysis of the factors which

may influence the surgeon's decision-making process for all locally advanced breast cancers and the T3 and T4 subgroup. These trends suggested that cases were more likely to be referred if the patient were younger (≤ 50 years), and/or had clinical lymph node involvement, and/or had AJCC stages IIIA, and/or had triple negative breast cancer. Though all cases within this subset should have been referred for neoadjuvant treatment, the presence of these factors did appear to aid in promoting the use of neoadjuvant referral. The information regarding molecular subtyping seemed especially important when the breast cancer in question was of the triple negative subtype. At present, receptor testing is not routinely performed on the needle core biopsy unless the surgeon requests it specifically. Therefore, unless the case is obviously a locally advanced breast cancer and the surgeon had the foresight to order receptor testing on the needle core biopsy, the surgeon cannot avail of the molecular subtype information to help with decision-making.

It is possible of course, that out of the seven cases with T3 and T4 tumors in 2016 which were not referred, age may have been the extenuating factor for at least one or two of these patients. In addition, the patient's right to choose with regards to the sequence of events surrounding their individual treatment must be honored as a legitimate reason not to refer. However, having approximately 40% of the eligible population not being referred for treatment which may potentially affect their overall survival should not be an acceptable outcome. Therefore, more must be done to promote the use of neoadjuvant treatment for surgeons who need to encourage eligible patients in order to maximize the treatment benefit at a curable stage.

Recommendations

The results of this evaluation project have revealed some underlying issues with the referral program and the clinical practice guideline program, as well. The referral rates for the entire locally advanced breast cancer cohort are much lower than the rates found in the literature review. However, the referral rates for the T3/T4 subgroup does fall within the literature's range for referral though a large proportion of patients (approximately 40%) who should have been referred, were not. These results also indicate that surgeons have failed to adhere to clinical practice guidelines regarding neoadjuvant therapy for the locally advanced breast cancer population. As investigator, insight into several of these issues have prompted the development of some recommendations to be initiated by the BDSG and the administrative body which may prove to be effective in combating these problems with an eye to improving patient outcomes.

The recommendations to improve referral rates from a systems approach include:

1. **Present the results to the administrative body** in the form of an executive summary, which highlights the issues within the healthcare system. Consulting those with extensive managerial expertise who are ideally positioned to offer advice and feedback on how to initiate change at a system level, is crucial;
2. **Present the results and issues to the Eastern Health BDSG** in order to encourage ideas and actions that can be initiated in-house in the respective departments to improve the availability of certain information which may affect the surgeons' decision-making ability. These include:
    - standardization of molecular subtype testing on all needle core breast biopsies of pathologically confirmed breast cancers;

- continuing to advocate for synoptic radiological and pathological reporting across the province;
- synoptic reporting of the decision-making process from surgeons;
- methods to increase the consultation and collaboration between surgeons and oncologists.

3. **Encourage the implementation of measures for professional development** among the guideline users and promotion of a team approach to patient care which include educational approaches which incorporate team-building tactics. The use of local conferences or workshops where oncologists can meet face-to-face with the province's family physicians and surgeons can be crucial in promoting the team approach, while providing interpretations of the latest research findings which are likely to change clinical practice.

There would be little argument that the referral process is highly complex and is often influenced by various factors. However, having studied many of these factors, it was determined that these factors alone, do not consistently influence decision-making. Clinical practice guidelines are meant to provide a resource for surgeons to consult when treatment decision-making is complicated or problematic. Yet, the evidence provided earlier indicates that surgeons often complain that guidelines are too long or too complex to enable ease of use. In the example of the Eastern Health BDSG, some physicians have complained about the difficulty in accessing or knowing where to access the guidelines.

The recommendations for improving the clinical practice guideline process, dissemination and uptake are:

1. **Carry out a survey of the province's surgeons** to determine what percentage are aware of or use the Eastern Health BDSG clinical practice guideline on neoadjuvant treatment. Also provide a summary of this evaluation project to engage surgeons by emphasizing the importance of participating in the survey and by giving them an opportunity to voice their opinions;
2. **Continue to provide evidence-based clinical practice guidelines** for surgeons and family physicians to guide the care of our patients diagnosed with breast cancer. However, it will be crucial going forward to develop guidelines that will incorporate the needs of the surgeons as highlighted in the survey;
3. **Revise the guidelines by** making them more user-friendly by clarifying the treatment options according to particular clinical situations. The introduction of treatment algorithms may be helpful to encourage family physicians and surgeons to utilize the guideline more frequently in the management of these patients. Two algorithms designed by the investigator are in Appendix B and C;
4. **Examine the dissemination practices** of our clinical practice guidelines in order to ensure that family physicians and surgeons are actually receiving them and are aware of, and familiar with the guidelines. Improving dissemination efforts may also be helpful in promoting the use of any newly developed treatment algorithms and potentially receiving feedback on their usefulness and improvement strategies.

Conclusion

The chart review process for this evaluation project was the crucial final step in gathering the best quality data available in order to answer the questions of interest in this study. The procedures and protocols implemented in this endeavor were essential in maintaining the internal validity of this project. Despite the measures taken however, the final sample size was too small to draw any firm conclusions for this study. Regardless of the sample size, it was still important to generate recommendations from the findings of this study. A complete year of patient data for the province had been used in both a pre- and post-guideline dissemination study period, even though the sample size was not sufficient. Increasing the sample size would require additional years of study which would have been limited by the small number of years in the post-dissemination period. In addition, recommendations were indeed necessary now especially since the referral rates were clearly lower than expected.

Nevertheless, it was possible to identify some trends in the data such as the presence of factors that were associated with the likelihood of referral to the medical oncology discipline. This project was useful in identifying the neoadjuvant referral rates which indicated a need for interventions which could increase the number of eligible patients being referred. It was also helpful in highlighting the need for a fundamental change in guideline development in order to make these guidelines more user-friendly, more accessible and more measurable for quality improvement initiatives. In addition, this project has provided a method which can be used as a template for evaluating other clinical practice guidelines developed by this group, or other groups.

The next steps for this project would be to develop and implement interventions as per the recommendations to ultimately increase the referral rate and to positively influence patient outcomes.

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Appendix A: AJCC Breast Cancer Staging

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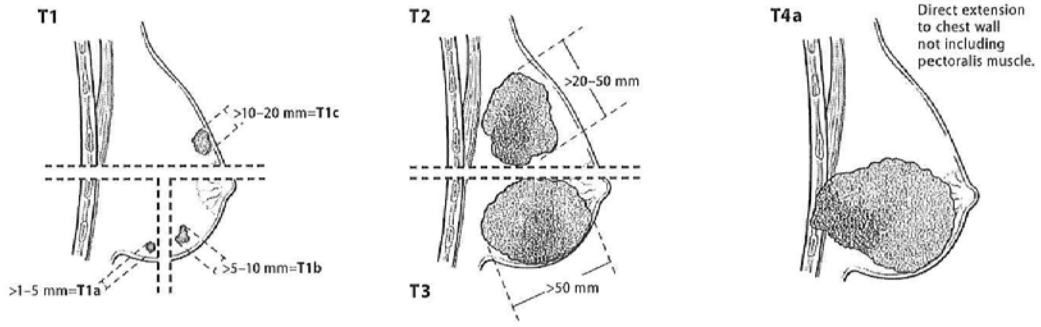
Breast Cancer Staging

7th EDITION



Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- Tis (DCIS) Ductal carcinoma in situ
- Tis (LCIS) Lobular carcinoma in situ
- Tis (Paget's) Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
- T1 Tumor ≤ 20 mm in greatest dimension
- T1mi Tumor ≤ 1 mm in greatest dimension
- T1a Tumor > 1 mm but ≤ 5 mm in greatest dimension
- T1b Tumor > 5 mm but ≤ 10 mm in greatest dimension
- T1c Tumor > 10 mm but ≤ 20 mm in greatest dimension
- T2 Tumor > 20 mm but ≤ 50 mm in greatest dimension
- T3 Tumor > 50 mm in greatest dimension
- T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

  Note: Invasion of the dermis alone does not qualify as T4
- T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion
- T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
- T4c Both T4a and T4b
- T4d Inflammatory carcinoma (see "Rules for Classification")

Distant Metastases (M)

- M0 No clinical or radiographic evidence of distant metastases
- cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes

* T1 includes T1mi.
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
+ M0 includes M0(i+).
# The designation pM0 is not valid; any M0 should be clinical.
^ If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
^ Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
^ Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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Breast Cancer Staging

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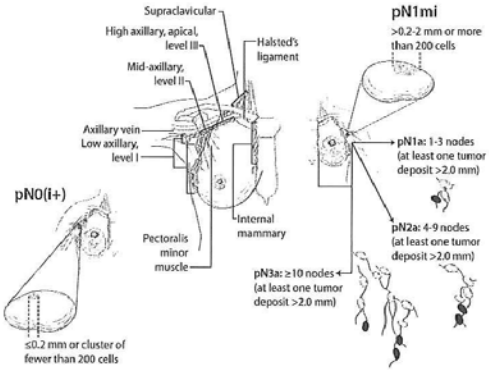
Regional Lymph Nodes (N)

CLINICAL

NX	Regional lymph nodes cannot be assessed (for example, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.



PATHOLOGIC (PN)*

pNX	Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
pN0(i–)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

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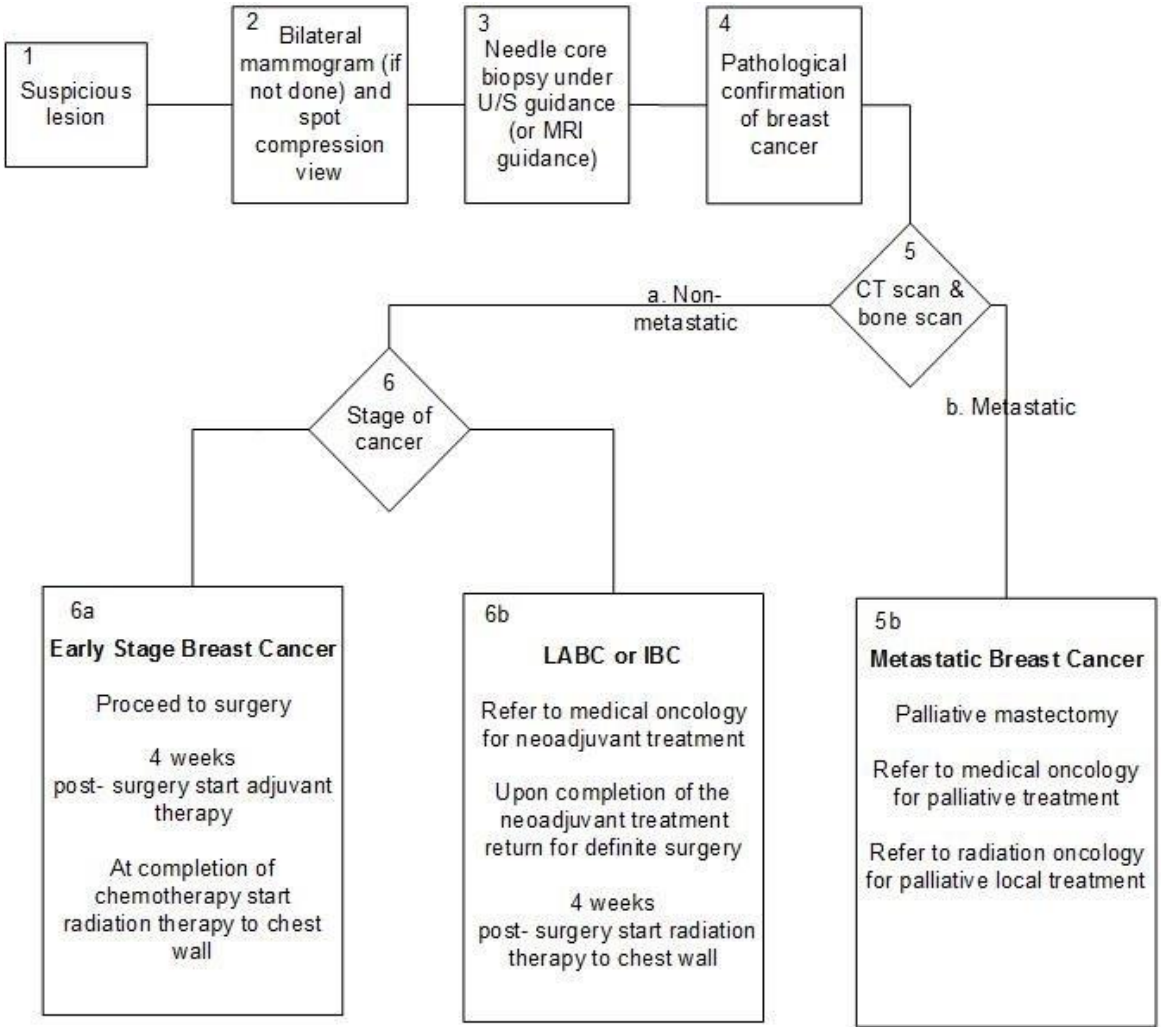
Appendix B: Diagnostic and Treatment Algorithm for Invasive Breast Cancer

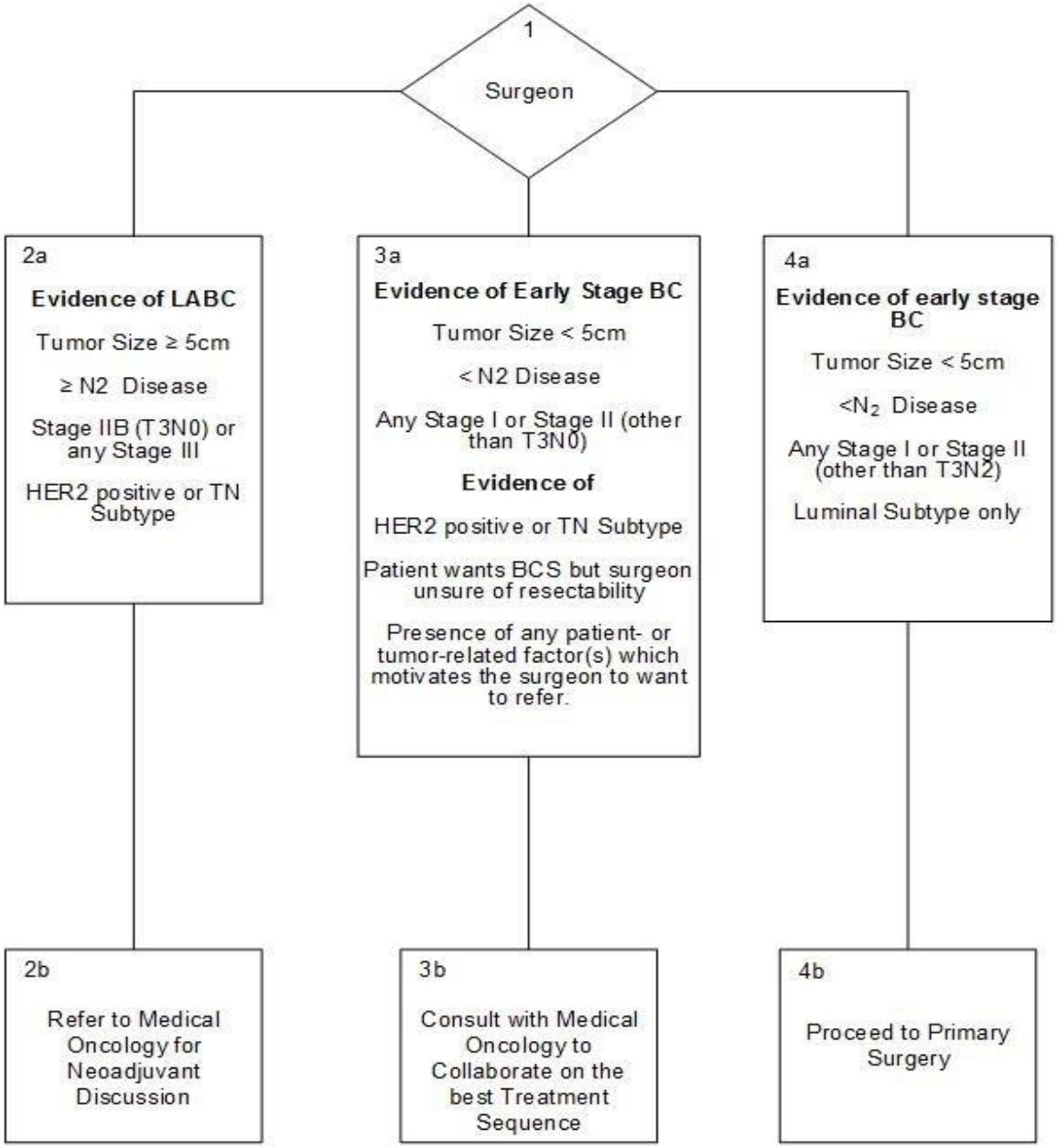


Legend for the Diagnostic and Treatment Algorithm for Invasive Breast Cancer

1. *Suspicious lesion:* Patients usually enter the oncology system with a suspicious breast lesion either through a clinical presentation (found by self or family physician), through the breast screening program (finding on routine screening mammogram), or through an incidental finding (found on imaging while being investigated for a different health issue, such as CT or MRI of chest).
2. *Bilateral mammogram and spot compression views:* A bilateral mammogram (if not already completed) and a spot compression view will be performed to evaluate the suspicious lesion.
3. *Needle core biopsy under ultrasound (or MRI) guidance:* If the lesion is still considered to be suspicious at this stage, a needle core biopsy is performed under ultrasound-guidance (or MRI-guidance when difficulty visualizing the lesion) in an attempt to establish whether the lesion is malignant or benign.
4. *Pathological confirmation of breast cancer:* The family physician will often consult a surgeon while waiting for the results, or once a pathological diagnosis of breast cancer has been confirmed.
5. *CT scan and bone scan:* During the first visit, the surgeon will order a CT scan of the chest, abdomen and pelvis as well as, a nuclear medicine bone scan to be performed to complete the cancer staging. The results of these tests will determine whether the patient has:
    a. *No evidence of metastatic disease:* See number 6.
    b. *Evidence of metastatic disease:* If imaging provides evidence of distant metastatic spread from the breast cancer primary to the bones or other organs, the surgeon may proceed with a palliative simple mastectomy and/or consult with both medical and radiation oncologists to determine the best treatment sequence with a palliative intent to alleviate symptoms and extend survival.

6. *No evidence of metastatic disease:* If imaging provides no definitive evidence of metastatic disease, the surgeon must determine to the best of her/his ability the AJCC clinical stage of the cancer. This will help determine whether the patient has in situ disease only, or if the patient has invasive disease which is either early stage or locally advanced/inflammatory breast cancer.
    a. *Early stage breast cancer:* If the surgeon determines the patient has early-stage breast cancer, then the patient will proceed to undergo adjuvant therapy consisting of definitive surgery first, followed by chemotherapy and/or endocrine therapy (for 5-10 years) post-operatively, followed by chest wall radiation therapy if indicated.
    b. *Locally advanced or inflammatory breast cancer:* If the surgeon determines the patient has locally advanced or inflammatory breast cancer, then the surgeon should refer the patient immediately to see a medical oncologist. If warranted, neoadjuvant chemotherapy or endocrine therapy will begin quickly, and the tumor will be assessed frequently for response. Sufficient tumor response after 4 to 6 cycles will be followed by definitive surgery, and then chest wall radiation therapy four week post-operatively. If there is little or no tumor response to the first treatment regimen after one or two cycles, the treatment can be altered or switched. Endocrine therapy will continue following the completion of radiation therapy for five to ten years, as directed.

Appendix C: Surgeon's Decision to Refer Algorithm



Legend for Surgeon's Decision to Refer for Non-Metastatic Invasive Breast Cancer

1. *Surgeon:* The surgeon must decide from the clinical, radiological and pathological evidence whether the patient has early stage breast cancer or has locally advanced/inflammatory breast cancer.

2a. *Locally advanced breast cancer or inflammatory breast cancer:* The surgeon would regard those patients with a clinical tumor size of ≥ 5 cm, and/or ≥ clinical N2 lymph node involvement, and/or a clinical AJCC stage IIB (T3N0) or any stage III breast cancer, with or without a HER2 positive or triple negative subtype on needle core biopsy to have locally advanced breast cancer. A patient with a clinical and pathological confirmation of inflammatory breast cancer will be regarded so by the surgeon.

2b. *Referral to Medical Oncology:* If the patient has been confirmed to have locally advanced breast cancer or inflammatory breast cancer as stipulated, the surgeon must refer the patient to the medical oncology discipline for a discussion about neoadjuvant therapy. The surgeon, using independent medical judgement, may decide to forego the neoadjuvant referral only in certain circumstances. One of these circumstances include when the patient's frailty or pre-existing co-morbidities impose an unacceptable mortality risk. Another would be when the patient refuses any treatment at all or will accept only surgical intervention. The surgeon must advise the patient of the risks of refusing some, or all, therapy and assure the patient that should change his/her mind the option of referral will still be open though the outcomes may not be assured.

3a. *Early stage breast cancer with extenuating circumstances:* The surgeon would regard patients to have early stage breast cancer if the patient had a clinical tumor size of < 5cm, and/or clinical N0 or N1 disease, and/or any clinical AJCC stage I or stage II (except T3 N0). However, patients with early breast cancer who have extenuating circumstances that may require neoadjuvant referral would include those with one or more of these clinical findings:

- a HER2 positive or triple negative subtype on needle core biopsy
- patient requests breast conserving surgery (BCS) but surgeon is unsure of resectability
- presence of any patient- or tumor-related factor(s) which may motivate the surgeon to refer (e.g., young age of patient, questionable clinical tumor size, grade 3 tumor, multifocal/multicentric disease).

3b. *Collaborate with a medical oncologist:* If the patient has any of the clinical findings listed in 3a, then the surgeon should contact a medical oncologist to present the case and come to some consensus of the best treatment sequence to initiate for the benefit of the patient.

4a. *Early stage breast cancer:* If the patient has a clinical tumor size of < 5cm, and/or clinical N0 or N1 disease, and/or any clinical AJCC stage I or stage II (except T3 N0) with or without a luminal subtype on needle core biopsy, then the surgeon must regard these cases as early stage breast cancer.

4b. *Proceed to primary surgery:* If the patient has no clinical indications which suggest the need for neoadjuvant referral than the surgeon must proceed to perform surgery has the primary treatment modality followed by a referral for adjuvant therapy approximately 4 weeks post-operatively.

Appendix D: Letter to Divisional Manager of the NL Cancer Registry

Dr. H. Bliss Cancer Center
300 Prince Philip Drive
St. John's, NL
709-777-8840
05/04/2018

Divisional Manager
NL Cancer Registry
Dr. H. Bliss Murphy Cancer Center
300 Prince Philip Drive
St. John's, NL

Dear Divisional Manager:

As per our discussion on March 2nd of this year, I am providing a written request for the specific data of interest for an evaluation project which does not require Health Research Ethics Authority approval. I have received permission from the Program Director of the Cancer Care Program to proceed with the above project. I am ready to begin the evaluation project on May 7th, 2018.

The sample population from which I will require data are:

- Female patients with a diagnosis of locally advanced breast cancer with the following clinical stages of IIB, IIIA, IIIB, IIIC, or a diagnosis of inflammatory breast cancer;
- Both years of 2013 and 2016 from January 1 to December 31 for each;
- Those who received neoadjuvant therapy as per sequence of primary surgery after chemotherapy or endocrine therapy.

The variables of interest required for this evaluation project are:

- Tumor size
- Histologic grade and type
- Unilateral versus bilateral
- Presence of multicentric or multifocal disease
- Estrogen and progesterone receptor status
- HER2 receptor status
- Clinical assessment of lymph node status
- Clinical AJCC staging
- Patient age
- Received neoadjuvant therapy (where possible)

Cynthia Higdon
Clinical Practice Guideline Coordinator

Appendix E: Data Collection Tool

Adherence to an Oncology Clinical Practice Guideline:
An Evaluation Project
Principal Investigator: Cynthia Higdon

Date: _____

Data Source: _____

PI Initials: _____

1. Subject medical care plan (MCP) number _____
2. Subject outpatient OPIS number (if needed) _____
3. Subject name (last, first) _____
4. Subject date of birth (mm/dd/yyyy) _____

Patient Demographic Data

5. Age at initial diagnosis _____
6. Year of initial diagnosis _____
7. Cancer diagnosis _____

Tumor-related Factors

8. Tumor size (mm) _____
9. Tumor histology _____
10. Tumor grade _____
11. Tumor laterality _____

Date: _____

Data Source: _____

PI Initials: _____

12. Tumor focality and/or centricity _____
13. Clinical lymph node status _____
14. AJCC staging _____
15. Molecular Subtyping
    a. Estrogen receptor (positive/negative, %) _____
    b. Progesterone receptor (positive/negative, %) _____
    c. Human epidermal growth factor (HER2) (positive/negative, rating) _____
    d. Subtype _____
    e. Testing specimen _____

Outcomes

16. Surgeon/family doctor referral _____
17. Treatment sequencing _____

Facility-related Data

18. Hospital name _____
19. Hospital type _____

Appendix F: Data Dictionary

Adherence to an Oncology Clinical Practice Guideline: An Evaluation Plan
Principal Investigator: Cynthia Higdon

Variable Name	Variable Description	Variable Definition
1. Patients' MCP number	Hospital medical record identifier number	Twelve-digit medical care plan number
2. Patients' OPIS number	DHBMCC 2013 medical chart identifier number	Eight-digit DHBMCC outpatient medical chart number
3. Patient name	Patient identifier	First and last name
4. Date of birth	Patient identifier	MM/DD/YYYY
5. Patient age	Age at initial diagnosis	Actual age in years
6. Year	Year of initial diagnosis	Actual calendar year diagnosed (2013 or 2016)
7. Cancer diagnosis	Confirmation of cancer diagnosis	Actual pathology-confirmed diagnosis on either needle core biopsy or surgically excised tumor (invasive mammary carcinoma or inflammatory breast cancer)
8. Neoajuvant therapy referral	Referral for neoadjuvant consideration	Whether the patient was referred to the medical oncology service for evaluation and consideration of neoadjuvant therapy; May be referred by surgeon or family doctor; Also considered referred if physician discussed case with a medical oncologist prior to surgical treatment; This is considered as either referred or not referred
9. Treatment sequence	Treatment sequencing received by patient	Actual treatment sequencing defined as either neoadjuvant (systemic therapy before definitive surgery) or adjuvant (definitive surgery before systemic therapy)
10. Size of tumor	Measurement of largest tumor foci	Actual measurement in millimeters (mm) of largest on tumor foci on palpation,

Variable Name	Variable Description	Variable Definition
		imaging or surgically excised tumor
11. Tumor histology	Type of breast cancer cell by location or notable feature	Identified as ductal, lobular, mixed (both ductal and lobular), medullary, mucinous, papillary, metaplastic, cribiform, sarcomatous, and inflammatory
12. Tumor grade	Description of the nature of the tumor cells	Denotes how closely the tumor cells appear in comparison to a normal breast cell (grade 1: well differentiated, grade 2: moderately differentiated, grade 3: poorly differentiated, or unknown: unable to assess)
13. Tumor laterality	Tumor involvement in one or both breasts	Pathological confirmation of tumor involvement isolated to one breast or in both breasts (unilateral or bilateral)
14. Tumor focality and/or multicentricity	Confirmation of number and location of tumor foci	Pathological or radiological confirmation of one or more tumor foci in one quadrant of the breast (unifocal or multifocal) or more than one quadrant of the breast (multicentric)
15. Clinical lymph node status	Clinical assessment of lymph node involvement	Pathological confirmation of surrounding lymph nodes which are, or radiologically appear to be, positive for tumor spread (negative or positive)
16. Chest wall and/or skin involvement	Tumor involvement of the chest wall and/or skin	Clinical, radiological or pathological evidence of tumor invasion into the chest wall and/or the skin (yes or no)
17. AJCC stage	Staging of disease by the American Joint Committee on Cancer	Clinical or pathological staging by TNM, where T is the tumor size in greatest dimension, Where N is the

Variable Name	Variable Description	Variable Definition
		level of lymph node involvement, and M is the presence or absence of distant metastases as per the AJCC staging manual in the appendix.
18. Estrogen receptor (ER) and/or progesterone receptor (PR)	Pathological detection of hormone receptors on surface of tumor cells	The presence of hormone receptors stimulates tumor cell growth; Presented has a percentage of pathologically detected cells with hormone receptors (0 to 100%): tumor cells with ≤ 10% staining considered negative, and those with > 10% staining considered positive; Use of antihormonal therapy may be warranted
19. Human epidermal growth factor receptor 2 (HER2 neu)	Pathological detection of an over-amplification of the HER2 neu receptor on surface of tumor cells	The presence of an over-amplification of HER2 neu receptors stimulates tumor cell growth; Presented as either HER2 1+ as a negative result and HER2 3+ as a positive result, while a HER2 2+ is an equivocal result which must undergo further testing (with FISH, CISH, or dual ISH tests to obtain one of the two initial results); Use of the monoclonal antibody, Herceptin may be warranted
20. Molecular subtype	The presence or absence of receptors on the cell surface which stimulate tumor cell growth; use of pharmaceutical intervention may be warranted	There are four common molecular subtypes of breast cancer which have been reduced to three types for this study: • Luminal A or B (presence of hormone receptors on the surface of the tumor

Variable Name	Variable Description	Variable Definition
		cells with or without the presence of an over-amplification of HER2 neu); • HER2 neu Positive (absence of hormone receptors but presence of an over-amplification of HER2 neu); and • Triple Negative (absence of hormone receptors and HER2 neu receptor amplification).
21. Molecular testing specimen	Specimen used for molecular testing	The tissue specimen used to test for ER, PR and HER2 neu receptors (needle core biopsy specimen or post surgically excised tumor specimen)
22. Hospital name	Hospital facility	Name of hospital facility where definitive surgery was performed which provides the location of the facility as well
23. Hospital type	By size and affiliation	Define the hospital has from a small, medium or large urban or small rural area; Also define has university-affiliated or community hospital

Appendix G: Cancer Registry Coding Guides

Breast

CS Tumor Size

- Note 1: Code the specific tumor size as documented in the medical record. If the only information regarding tumor size is the physician's statement of the T category, assign code 990 (T1mi), 991 (T1b), 992 (T1 or T1c), or 995 (T2). If the physician's statement of the T category is T1a with no documentation of tumor size, code tumor size as 005. If the physician's statement of the T category is T3 with no documentation of tumor size or a statement specifying only that the tumor size is greater than 5 cm, code tumor size as 051.

- Note 2: When coding pathologic size, code the measurement of the invasive component. For example, if there is a large in situ component (e.g., 4 cm) and a small invasive component, see CS Site-Specific Factor 6 to code more information about the reported tumor size. If the size of invasive component is not given, code the size of the entire tumor and record what the size value represents in CS Site-Specific Factor 6. Note that some breast cancers cannot be sized pathologically

- Note 3: Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.)

Code	Description
000	No mass/tumor found
001-988	001 - 988 millimeters (mm) (Code exact size in mm)
989	989 mm or larger
990	Microinvasion Microscopic focus or foci only and no size given Described as "less than 1 mm" Stated as T1mi with no other information on tumor size
991	Described as "less than 1 centimeter (cm)" Stated as T1b with no other information on tumor size

992	Described as "less than 2 cm," or "greater than 1 cm," or "between 1 cm and 2 cm" Stated as T1 [NOS] or T1c [NOS] with no other information on tumor size
993	Described as "less than 3 cm," or "greater than 2 cm," or "between 2 cm and 3 cm"
994	Described as "less than 4 cm," or "greater than 3 cm," or "between 3 cm and 4 cm"
995	Described as "less than 5 cm," or "greater than 4 cm," or "between 4 cm and 5 cm" Stated as T2 with no other information on tumor size
996	Mammographic/xerographic diagnosis only, no size given; clinically not palpable
997	Paget disease of nipple with no demonstrable tumor
998	Diffuse
999	Unknown; size not stated Size of tumor cannot be assessed Not documented in patient record

List of Schemas Breast Schema Index

HER 2 neu	Value
00	IHC1^{+}
01	IHC2^{+}
02	IHC3^{+}
03	IHC^{-}
04	FISH^{+}
05	FISH^{-}
06	CISH^{+}
07	CISH^{-}
08	SISH^{+}
09	SISH-
10	Dual ISH^{+}

ER/PR	
01	Positive
02	Negative

Blank Fields	No data available

T Size	mm

999	unknown

Breast

CS Lymph Nodes

Note 1: Code only regional nodes and nodes, NOS, in this field. Distant nodes such as cervical (excluding supraclavicular) or contralateral axillary are coded in CS Mets at DX.

Note 2: Micrometastases are defined as tumor deposits greater than 0.2 millimeter (mm) but not greater than 2.0 mm in largest dimension. Macrometastases are tumor deposits greater than 2.0 mm. All nodes with at least micrometastases are included in the count of positive lymph nodes, but at least one node must contain a macrometastasis for assignment of a pathologic N category greater than pN1mi.

Note 3: If the pathology report indicates that nodes are positive, but size of the metastases is not stated, assume the metastases are greater than 0.2 mm and code the lymph nodes as positive in this field. Use code 600 in the absence of other information about regional nodes.

Note 4: In a physical exam if palpable nodes are not described as fixed or matted, assume that nodes are movable.

Note 5: Codes 130-600 refer to level I and level II ipsilateral axillary lymph nodes and ipsilateral intramammary nodes only. Ipsilateral level Ill axillary lymph nodes, which are also known as infraclavicular or apical nodes, are coded 750 or higher. Axillary lymph nodes do not include internal mammary or ipsilateral supraclavicular lymph nodes.

Note 6: For the breast schema, the choice of the N category is dependent on the CS Lymph Nodes Eval field. There are certain CS Lymph Nodes codes that can only be used if the nodes are evaluated clinically (CS Lymph Nodes Eval is coded 0, 1, 5, or 9), which will be designated as "Evaluated clinically:" at the beginning of the code description. Similarly, there are certain CS Lymph Nodes codes that can only be used if the nodes are evaluated pathologically (CS Lymph Nodes Eval is coded 2, 3, 6, or 8), and these will be designated as "Evaluated pathologically:". All other codes can be used for clinical or pathologic evaluation.

Note 7: Isolated tumor cells (ITC) are defined as single tumor cells or small clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on hematoxylin and eosin (H and E) stains. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction). Lymph nodes with ITCs only are not considered positive lymph nodes. If the record only states N0(i+), code to 000 and see CS Site-Specific Factor 4.

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
000	No regional lymph node involvement OR isolated tumor cells (ITCs) detected by immunohistochemistry/ immunohistochemical: (IHC) methods or molecular methods ONLY. (See Note 7 and CS Site-Specific Factors 4 and 5)	^ .	*	NONE	NONE
050	Evaluated pathologically: None; no regional lymph node involvement BUT ITCs detected on routine hematoxylin and eosin (H and E) stains. (See Note 7)	N0(i+)	N0(i+)	NONE	NONE
130	Evaluated pathologically: Axillary lymph node(s), ipsilateral, micrometastasis ONLY detected by IHC ONLY (At least one micrometastasis greater than 0.2 mm or more than 200 cells AND all micrometastases less than or equal to 2 mm)	N1mi	N1mi	RN	RN
150	Evaluated pathologically: Axillary lymph node(s), ipsilateral, micrometastasis ONLY detected or verified on H&E (At least one micrometastasis greater than 0.2 mm or more than 200 cells AND all micrometastases less than or equal to 2 mm) Micrometastasis, NOS	N1mi	N1mi	RN	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
155	Evaluated pathologically: Stated as N1mi with no other information on regional lymph nodes	N1mi	N1mi	RN	RN
250	Evaluated pathologically: Movable axillary lymph node(s), ipsilateral, positive with more than micrometastasis (At least one metastasis greater than 2 mm) (See Note 4)	^^	**	RN	RN
255	Evaluated pathologically: Clinically movable axillary lymph node(s), ipsilateral, positive (Clinical assessment because of neoadjuvant therapy or no pathology) (See Note 4)	N1	N1	RN	RN
257	Evaluated pathologically: Clinically stated only as N1 (Clinical assessment because of neoadjuvant therapy or no pathology)	N1	N1	RN	RN
258	Evaluated pathologically: Pathologically stated only as N1 [NOS], no information on which nodes were involved	^^	**	RN	RN
260	Stated as N1 [NOS] with no other information on regional lymph nodes	^^	**	RN	RN
280	OBSOLETE DATA RETAINED V0104 Stated as N2, NOS	ERROR	**	RN	RN
290	OBSOLETE DATA CONVERTED V0203 See code 610 Clinically stated only as N2,	ERROR	ERROR	ERROR	ERROR

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
	NOS (clinical assessment because of neoadjuvant therapy or no pathology)				
300	OBSOLETE DATA CONVERTED V0203 See code 620 Pathologically stated only as N2, NOS; no information on which nodes were involved	ERROR	ERROR	ERROR	ERROR
500	OBSOLETE DATA RETAINED V0104 Fixed/matted ipsilateral axillary nodes, positive with more than micrometastasis (i.e., at least one metastasis greater than 2 mm) Fixed/matted ipsilateral axillary nodes, NOS	ERROR	**	RN	RN
510	Evaluated clinically: Fixed/matted ipsilateral axillary nodes Clinically (Clinical assessment because of neoadjuvant therapy or no pathology) Stated clinically as N2a (Clinical assessment because of neoadjuvant therapy or no pathology)	^^	**	RN	RN
520	Evaluated pathologically: Fixed/matted ipsilateral axillary nodes clinically with pathologic involvement of lymph nodes WITH at least one metastasis greater than 2mm	^^	**	RN	RN
600	Axillary/regional lymph	^^	**	RN	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
	node(s), NOS Lymph nodes, NOS				
610	Evaluated clinically: Clinically stated only as N2 [NOS] (Clinical assessment because of neoadjuvant therapy or no pathology)	^^	**	RN	RN
620	Evaluated path0l0gically: Pathologically stated only as N2 [NOS]; no information on which nodes were involved	^^	**	RN	RN
630	Stated as N2 [NOS] with no other information on regional lymph nodes	^^	**	RN	RN
710	Evaluated pathologically: Internal mammary node(s), ipsilateral, positive on sentinel nodes but not clinically apparent (No positive imaging or clinical exam) WITHOUT axillary lymph node(s), ipsilateral	N1b	N1b	RN	RN
720	Evaluated pathologically: Internal mammary node(s), ipsilateral, positive ·on sentinel nodes but not clinically apparent (No positive imaging or clinical exam) WITH axillary lymph node(s), ipsilateral	^^	**	RN	RN
730	Evaluated pathologically: Internal mammary node(s), ipsilateral, positive on sentinel nodes but not clinically apparent (No positive imaging or clinical exam)	N1b	N1b	RN	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
	UNKNOWN if positive axillary lymph node (s), ipsilateral				
735	Evaluated clinically: Internal mammary node(s), ipsilateral, positive on sentinel nodes but primary not resected WITHOUT axillary lymph node(s), ipsilateral OR UNKNOWN if positive axillary lymph node(s)	N2b	N2b	RN	RN
740	Internal mammary node(s), ipsilateral, clinically apparent (On imaging or clinical exam) WITHOUT axillary lymph node(s), ipsilateral	N2b	N2b	RN	RN
745	Internal mammary node(s), ipsilateral, clinically apparent (On imaging or clinical exam) UNKNOWN if positive axillary lymph node (s), ipsilateral	N2b	N2b	RN	RN
748	Stated as N2b with no other information on regional lymph nodes	^^	**	RN	RN
750	Infraclavicular lymph node(s) (subclavicular) (level lll axillary nodes) (apical), ipsilateral WITH or WITHOUT axillary nodes(s) WITHOUT internal mammary node(s)	N3a	N3a	D	RN
755	Stated as N3a with no other information on regional lymph nodes	N3a	N3a	D	RN
760	OBSOLETE DATA RETAINED AND	N3b	N3b	RN	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
	REVIEWED V0203 See codes 763 and765 Internal mammary node(s), ipsilateral, clinically apparent (on imaging or clinical exam) WITH axillary lymph node(s), ipsilateral, codes 150 to 600 WITH or WITHOUT infraclavicular (Ievel III axillary nodes) (apical) lymph nodes				
763	Internal mammary node(s), ipsilateral, clinically apparent (On imaging or clinical exam). WITH axillary lymph node(s), ipsilateral, codes 150 to 600 WITHOUT infraclavicular (level Ill axillary nodes) (apical) lymph nodes or unknown if infraclavicular (level Ill axillary nodes) ;' (apical) lymph nodes involved	N3b	N3b	RN	RN
764	Internal mammary node(s), ipsilateral, clinically apparent (On imaging or clinical exam) WITHOUT axillary lymph node(s), ipsilateral WITH infraclavicular (level Ill axillary nodes) (apical) lymph nodes involved	N3b	N3b	D	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
765	Internal mammary node(s), ipsilateral, clinically apparent (On imaging or clinical exam) WITH axillary lymph node(s), ipsilateral WITH infraclavicular (level lll axillary nodes) (apical) lymph nodes involved	N3b	N3b	D	RN
768	Stated as N3b with no other information on regional lymph nodes	N3b	N3b	RN	RN
770	OBSOLETE DATA RETAINED V0200 Internal mammary node(s), ipsilateral, clinically apparent (on imaging or clinical exam) UNKNOWN if positive axillary lymph node (s), ipsilateral	ERROR	N2b	RN	RN
780	OBSOLETE DATA RETAINED V0200 (750) + (770)	ERROR	N3a	D	RN
790	OBSOLETE DATA CONVERTED V0203 See code 820 Stated as N3, NOS	ERROR	ERROR	ERROR	ERROR
800	Supraclavicular node(s), ipsilateral	N3c	N3c	D	D
805	Stated as N3c with no other information on regional lymph nodes	N3c	N3c	D	D
810	Evaluated clinically: Clinically stated only as N3 [NOS] (Clinical assessment because of	N3NOS	N3NOS	RN	RN

Code	Description	TNM 7 Map	TNM 6 Map	SS77 Map	SS2000 Map
	neoadjuvant therapy or no pathology)				
815	Evaluated pathologically: Pathologically stated only as N3 [NOS]; no information on which nodes were involved	N3NOS	N3NOS	RN	RN
820	Stated as N3, NOS with no other information on regional lymph nodes	N3NOS	N3NOS	RN	RN
999	Unknown; regional lymph nodes not stated Regional lymph node(s) cannot be assessed Not documented in patient record	NX	NX	U	U

^For CS Lymph Nodes code 000 ONLY, the N category is assigned based on the coding of CS Site-Specific Factors 4 and 5 using the IHC MOL Table for this schema.

^^For CS Lymph Nodes codes 250, 258, 260, 510, 520, 600, 610, 620, 630, 720, and 748 ONLY, the N category is assigned based on the values of CS Lymph Nodes Eval and CS Site-Specific Factor 3 (Number of Positive Ipsilateral Axillary Lymph Nodes). If the CS Lymph Nodes Eval code is 2(p), 3(p), 6(yp), or 8(a), the N category is determined by reference to the Lymph Nodes Pathologic Evaluation Table. If the CS Lymph Nodes Eval code is 0(c), 1(c), 5(c), or 9(c), the N category is determined by reference to the Lymph Nodes Clinical Evaluation Table. If the CS Lymph Nodes Eval field is not coded, the N category is determined by reference to the Lymph Nodes Positive Axillary Node Table.

*For CS Lymph Nodes code 000 ONLY, the N category is assigned based on the coding of CS Site-Specific Factors 4 and 5 using the IHC MOL Table for this schema.

**For CS Lymph Nodes codes 250, 258, 260, 280, 500, 510, 520, 600, 610, 620, 630, 720, and 748 ONLY, the N category is assigned based on the values of CS Lymph Nodes Eval and CS Site-Specific Factor 3 (Number of Positive Ipsilateral Axillary Lymph Nodes). If the CS Lymph Nodes Eval code is 2(p), 3(p), 6(yp), or 8(a), the N category is determined by reference to the Lymph Nodes Pathologic

Evaluation Table. If the CS Lymph Nodes Eval code is 0(c), 1(c), 5(c), or 9(c), the N category is determined by reference to the Lymph Nodes Clinical Evaluation Table. If the CS Lymph Nodes Eval field is not coded, the N category is determined by reference to the Lymph Nodes Positive Axillary Node Table.

Breast

CS Lymph Nodes Eval

- Note 1: This field is used primarily to derive the staging basis for the N category in the TNM system. It records how the code for the item "CS Lymph Nodes" was determined based on the diagnostic methods employed and their intent.

- Note 2: In the 7th edition of the AJCC manual, the clinical and pathologic classification rules for the N category were changed to reflect current medical practice. The N is designated as clinical or pathologic based on the intent (workup versus treatment) matching with the assessment of the T classification. When the intent is workup, the staging basis is clinical, and when the intent is treatment, the staging basis is pathologic.

    A. Microscopic assessment including biopsy of regional nodes or sentinel nodes if being performed as part of the workup to choose the treatment plan, is therefore part of the clinical staging. When it is part of the workup, the T category is clinical, and there has not been a resection of the primary site adequate for pathologic T classification (which would be part of the treatment).

    B. Microscopic assessment of regional nodes if being performed as part of the treatment is therefore part of the pathologic staging. When it is part of the treatment, the T category is pathologic, and there has been a resection of the primary site adequate for pathologic T classification (all part of the treatment).

- Note 3: Microscopic assessment of the highest N category is always pathologic (code 3).

- Note 4: If lymph node dissection is not performed after neoadjuvant therapy, use code 0 or 1.

- Note 5: Only codes 5 and 6 are used if the node assessment is performed after neoadjuvant therapy.

Code	Description	Staging Basis
0	Does not meet criteria for AJCC ·pathologic staging: No regional lymph nodes removed for examination. Evidence based on physical examination, imaging examination, or other non-invasive clinical evidence. No autopsy evidence used.	c
1	Does not meet criteria for AJCC pathologic staging based on at least one of the following criteria: No regional lymph nodes removed for examination. Evidence based on endoscopic examination, or other invasive techniques including surgical observation, without biopsy. No autopsy evidence used. OR Fine needle aspiration, incisional core needle biopsy, or excisional biopsy of regional lymph nodes or sentinel nodes as part of the diagnostic workup, WITHOUT removal of the primary site adequate for pathologic T classification (treatment).	c
2	Meets criteria for AJCC pathologic staging: No regional lymph nodes removed for examination, but evidence derived from autopsy (tumor was suspected or diagnosed prior to autopsy).	p
3	Meets criteria for AJCC pathologic staging based on at least one of the following criteria: Any microscopic assessment of regional nodes (including FNA, incisional core needle bx, excisional bx, sentinel node bx or node resection), WITH removal of the primary site adequate for pathologic T classification·(treatment) or biopsy assessment of the highest T category. OR Any microscopic assessment of a regional node in the highest N category, regardless of the T category information.	p
5	Does not meet criteria for AJCC y-pathologic (yp) staging: Regional lymph nodes removed for examination AFTER neoadjuvant therapy AND lymph node evaluation based	c

Code	Description	Staging Basis
	on clinical evidence, unless the pathologic evidence at surgery (AFTER neoadjuvant) is more extensive (see code 6).	
6	Meets criteria for AJCC y-pathologic (yp) staging: Regional lymph nodes removed for examination AFTER neoadjuvant therapy AND lymph node evaluation based on pathologic evidence, because the pathologic evidence at surgery is more extensive than clinical evidence before treatment.	yp
8	Meets criteria for AJCC autopsy (a) staging: Evidence from autopsy; tumor was unsuspected or undiagnosed prior to autopsy.	a
9	Unknown if lymph nodes removed for examination Not assessed; cannot be assessed Unknown if assessed Not documented in patient record	c

Appendix H: Health Research Ethics Authority Screening Tool

	Question	Yes	No
1.	Is the project funded by, or being submitted to, a research funding agency for a research grant or award that requires research ethics review?	❒	☒
2.	Are there any local policies which require this project to undergo review by a Research Ethics Board?	❒	☒
	IF YES to either of the above, the project should be submitted to a Research Ethics Board. **IF NO** to both questions, continue to complete the checklist.	❒	☒
3.	Is the primary purpose of the project to contribute to the growing body of knowledge regarding health and/or health systems that are generally accessible through academic literature?	❒	☒
4.	Is the project designed to answer a specific research question or to test an explicit hypothesis?	❒	☒
5.	Does the project involve a comparison of multiple sites, control sites, and/or control groups?	❒	☒
6.	Is the project design and methodology adequate to support generalizations that go beyond the particular population the sample is being drawn from?	❒	☒
7.	Does the project impose any additional burdens on participants beyond what would be expected through a typically expected course of care or role expectations?	❒	☒
LINE A: SUBTOTAL Questions 3 through 7 = (Count the # of Yes responses)		**0**	**7**
8.	Are many of the participants in the project also likely to be among those who might potentially benefit from the result of the project as it proceeds?	❒	☒
9.	Is the project intended to define a best practice within your organization or practice?	☒	❒
10.	Would the project still be done at your site, even if there were no opportunity to publish the results or if the results might not be applicable anywhere else?	☒	❒
11.	Does the statement of purpose of the project refer explicitly to the features of a particular program, organization, or region, rather than using more general terminology such as rural vs. urban populations?	☒	❒
12.	Is the current project part of a continuous process of gathering or monitoring data within an organization?	☒	❒
LINE B: SUBTOTAL Questions 8 through 12 = (Count the # of Yes responses)		**4**	**1**
	SUMMARY **See Interpretation Below: Line B = 4 > Line A = 0 Quality/Evaluation**		

- If the sum of Line A is greater than Line B, the most probable purpose is **research**. The project should be submitted to an REB.
- **If the sum of Line B is greater than Line A, the most probable purpose is quality/evaluation. Proceed with locally relevant process for ethics review (may not necessarily involve an REB).**
- If the sums are equal, seek a second opinion to further explore whether the project should be classified as Research or as Quality and Evaluation.

These guidelines are used at Memorial University of Newfoundland and were adapted from ALBERTA RESEARCH ETHICS COMMUNITY CONSENSUS INITIATIVE (ARECCI). Further information can be found at: http://www.hrea.ca/Ethics-Review-Required.aspx.

NOTE: Since the YES answers are greater in Line B (4) than those in Line A (0), this indicates that this practicum project is likely to be a Quality Initiative or Evaluation Project.

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Appendix E: Executive Summary

ADHERENCE TO AN EASTERN HEALTH NEOADJUVANT BREAST CANCER CLINICAL PRACTICE GUIDELINE

A NL Cancer Care Program Report

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ADHERENCE TO AN EASTERN HEALTH NEOADJUVANT BREAST CANCER CLINICAL PRACTICE GUIDELINE

Background

In the fall of 2017 during a regularly scheduled monthly meeting, concerns were being raised by some members of the Eastern Health Breast Disease Site Group (BDSG). The concerns brought forth were regarding whether breast cancer patients, eligible for neoadjuvant therapy, were being appropriately referred to the medical oncology discipline by their surgeons. Neoadjuvant therapy is the standard of care for patients diagnosed with locally advanced breast cancer (LABC) or inflammatory breast cancer (IBC), and is recommended by the Eastern Health BDSG clinical practice guideline "*Neoadjuvant Treatment of Primary Breast Cancer"*. This clinical practice guideline was approved in July 2014 and disseminated to all surgeons who perform breast surgery in the province of Newfoundland and Labrador (NL).

An active member of the BDSG, I am presently employed in the position of Clinical Practice Guideline Coordinator at the Dr. H. Bliss Murphy Cancer Center (DHBMCC). As part of the fulfillment of the requirements of the Master of Nursing Program at the Graduate School of Nursing, I had offered the BDSG the opportunity to use my practicum as a means with which to assess adherence to an Eastern Health pre-existing clinical practice guideline. The membership decided that a study should be conducted to evaluate the proportion of patients, eligible for neoadjuvant therapy, who received a referral to medical oncology and whether any change had occurred since the dissemination of guideline.

Three approaches were used to gather the information required to carry out this program evaluation. A comprehensive literature review was conducted, consultations were carried out with key individuals with expertise in their fields, and an extensive retrospective chart review was performed. The full report prepared for this evaluation project is available in the Memorial University Health Sciences Library research repository.

The program director of the NL Cancer Care Program granted permission for conducting this program evaluation project and access to patient information from the medical charts of the DHBMCC and the NL Cancer Registry database.

Literature Review

A comprehensive literature review was performed to obtain research evidence on the use of neoadjuvant therapy, adherence to clinical practice guidelines and factors that may affect the surgeons' decision to refer. Four research studies related specifically to neoadjuvant therapy and guideline adherence, as well as 35 general breast cancer-related

studies about guideline adherence, were obtained. The four neoadjuvant studies provided the evidence for a range of neoadjuvant referral rates for both cohorts of interest. The evidence suggested that the rate of neoadjuvant referrals for those with LABC was in the range of 44% to 79%, while the rate for those with IBC was in the range of 72% to 93%.[1,2,3,4]

Additional information acquired from these literature reviews included strategies to improve the rigor and internal validity of this evaluation project; variables of interest which may influence the decision-making process including patient demographics, tumor characteristics, and facility type and location; and suggestions for variable measurement. Though a preliminary list of variables of interest were identified at this stage, adjustments were made to the list to accommodate data availability during the chart review process.

The outcomes of interest were the referral rates pre and post guideline dissemination according to diagnosis and study period and which patient/tumor/facility-related variables impacted the surgeons' decision to pursue a medical oncology referral.

Consultations

An interview with two medical oncologists provided necessary information to finalize the eligibility criteria for the study, which were based on the definitions used in the BDSG guideline. The IBC cohort is a T4 subtype of LABC and is reported separately due to its distinct aggressive biology and clinical presentation. The LABC cohort were categorized as having at least one of three characteristics:

- at least one tumor having a size greater than 5cm;
- the presence of clinically palpable, or radiological imaging, of ipsilateral axillary lymph nodes or ipsilateral internal mammary nodes in keeping with at least level II lymph nodes (N2); or
- breast cancer stages of either IIB (T3 N0 M0 only), or any stage III.

An interview with a surgeon provided additional information on the various factors or variables which can affect the decision to refer the patient for neoadjuvant consideration or proceed to primary surgical options. Some of these variables included patient demographics such as age, health status and co-morbidities, interest in breast conservation therapy; several tumor characteristics such as tumor size, histology, grade and molecular subtype; and the type of facility, either a university-affiliated hospital or community-based hospital.

After the consultation with the director of the NL Cancer Registry, the study time periods of interest were defined as the full calendar year of 2013 and 2016, representing the pre and post dissemination phases. The interview also provided beneficial information on the identification of the various data sources required depending on the study year. The

interview with the ARIA computer support person was helpful in providing the necessary training for collecting the data from this system.

Chart Review

Methods

The patient data were extracted from the NL Cancer Registry by the registry director and I extracted any remaining data of interest from the chart review. All data were documented into Excel spreadsheets and any analysis was conducted in Excel. This project was determined to be a program evaluation for quality improvement purposes and therefore exempt from Health Research Ethics Board review.

Results and Discussion

The Cancer Registry provided data on 113 patient cases in 2013 and 133 in 2016. Sixty-six cases were ineligible in the 2013 sample and 79 were ineligible in the 2016 sample. The reasons for ineligibility included cases with metastatic disease, inappropriate cancer stages, and male cases. In 2013, the final sample consisted of four cases of IBC and 43 cases of LABC while in 2016, there were two cases of IBC and 52 cases of LABC.

All six cases of IBC in 2013 and 2016 were referred to medical oncology for neoadjuvant therapy. Though the sample numbers were very small, these results suggest that surgeons referred 100% of the IBC cases for neoadjuvant treatment at least for the two years studied.

The referral rates were calculated for all patient cases diagnosed with LABC and an additional analysis was conducted for a subset of the LABC sample, the patient cases with T3 and T4 tumors. The T3/T4 subgroup, by definition, automatically should have been referred by their surgeon for neoadjuvant therapy and therefore was felt to reflect a more meaningful referral rate than that obtained for all LABC cases. Table 1 summarizes the referral rates for both the LABC group and T3/T4 subgroup. The referral rate for all LABC patient cases was 23.3% in 2013 and 26.9% in 2016 while the referral rate for the T3/T4 subset was 66.7% in 2013 and 61.1% in 2016. The referral rate for all LABC cases was much lower than the range identified from the literature of 44% to 79% while the rate for the T3/T4 tumors falls within it. Nevertheless, nearly 40% of the eligible T3/T4 patient cases of the LABC population were not referred to medical oncology for a discussion regarding neoadjuvant therapy in 2016.

These results also indicated that there was little or no difference in referral rates between pre- and post-guideline dissemination which indicates that the BDSG guideline has had little effect on the number of patients being referred for neoadjuvant consideration.

Table 1: *Number and Proportion of All Patients with T3/T4 Tumors and All Locally Advanced Breast Cancers (LABC) According to Referral Status in 2013 and 2016*

Locally Advanced Breast Cancer	**2013 N = 43**		**Total n (%)**	**2016 N = 52**		**Total n (%)**
	Referred n (%)	**Not Referred n (%)**		**Referred n (%)**	**Not Referred n (%)**	
All	10 (23.3%)	33 (76.7%)	43 (100%)	14 (26.9%)	38 (73.1%)	52 (100%)
T3	5(55.6%)	3(33.3%)	9 (20.9%)	9(50.0%)	6(33.3%)	18 (34.6%)
T4	1(11.1%)	0(0)		2(11.1%)	1(5.6%)	

A final analysis was conducted on the T3/T4 subgroup in 2016 to investigate whether any of the variables studied appear to have influenced the surgeons' decision to refer. The small sample size prevented the use of multivariable analysis to determine whether any of the chosen independent variables were positively associated with the likelihood of being referred. However, several trends were identified in the data which indicated that certain subsets of the T3/T4 subgroup seemed more likely to be referred for neoadjuvant consideration. Table 2 summarizes only those variables which appeared to demonstrate trends in the T3/T4 data. These subsets consisted of younger patients, those surgically treated at university-affiliated hospitals, positive lymph node involvement, a clinical diagnosis of Stage IIIA and IIIC breast cancers, and triple negative subtype.

Table 2: *Patient/Tumor/Facility-related Variables of Clinical T3/T4 Tumors of LABC by Referral Status for 2016*

Variables	**Referred n = 11**	**Not Referred n = 7**
Age Range (in years)	**Median Age: 54 Range: 34 to 79**	**Median Age: 55 Range: 33 to 85**
41 – 50	4	1
Facility Type		
Large Urban (University-affiliated)	6	3
Lymph Node Status		
Positive	11	5

Variables	Referred n = 11	Not Referred n = 7
AJCC Stage (Clinical or Pathological)		
Stage IIIA	7	4
Stage IIIC	4	0
Molecular Subtype		
Triple Negative	6	1

Recommendations

There is an obvious need to implement measures which are intended to improve the rates of neoadjuvant referral and improve outcomes for our eligible patients with LABC, especially for those with HER2 positive and tripe negative subtypes. The following are a list of recommendations that are for discussion to bring about a positive change in compliance rates for surgeons. The recommendations are:

1. Determine measures that can be taken in-house to improve the neoadjuvant referral rates such as:
   a. encourage more opportunities for consultation and collaboration;
   b. improve the advertisement regarding tumor boards and how to access them for presentation of patient cases;
   c. improve accessibility to a medical oncologist; and
   d. promote receptor testing on needle core biopsy specimens so the surgeon has this information at the time of decision-making.

2. Implement measures for professional development and promote a team approach among oncologists, surgeons and family physicians to ultimately improve patient care, for example:
   a. educational events such as conferences, workshops or written updates of new research findings requiring changes in practice;
   b. encourage surgeons to participate in efforts to improve the rate of neoadjuvant referral for eligible patients; and
   c. maintain focus on team-building efforts to build consensus and encourage collaboration on the appropriate approach.

3. Implement measures to improve the usability and use of the BDSG neoadjuvant guideline such as:
   a. conduct a survey for surgeons and family doctors about the BDSG clinical practice guidelines;
   b. shorten and simplify the guidelines and use algorithms to clarify decision-making options, examples of which are provided in Appendix A and B; and

c. re-examine the methods for dissemination of the BDSG guidelines to determine if surgeons and family physicians are receiving them.

Conclusion

This practicum project has been successful in evaluating the state of neoadjuvant referrals by surgeons in this province. Although the results were less than desirable, it has provided the opportunity for the BDSG and the administrative body to help initiate measures which can bring about change. It is also clear that measures must be taken to improve the effectiveness of our clinical practice guidelines. It will require the input from and collaboration between all key stakeholders to create the change needed to improve outcomes for our locally advanced and inflammatory breast cancer patients.

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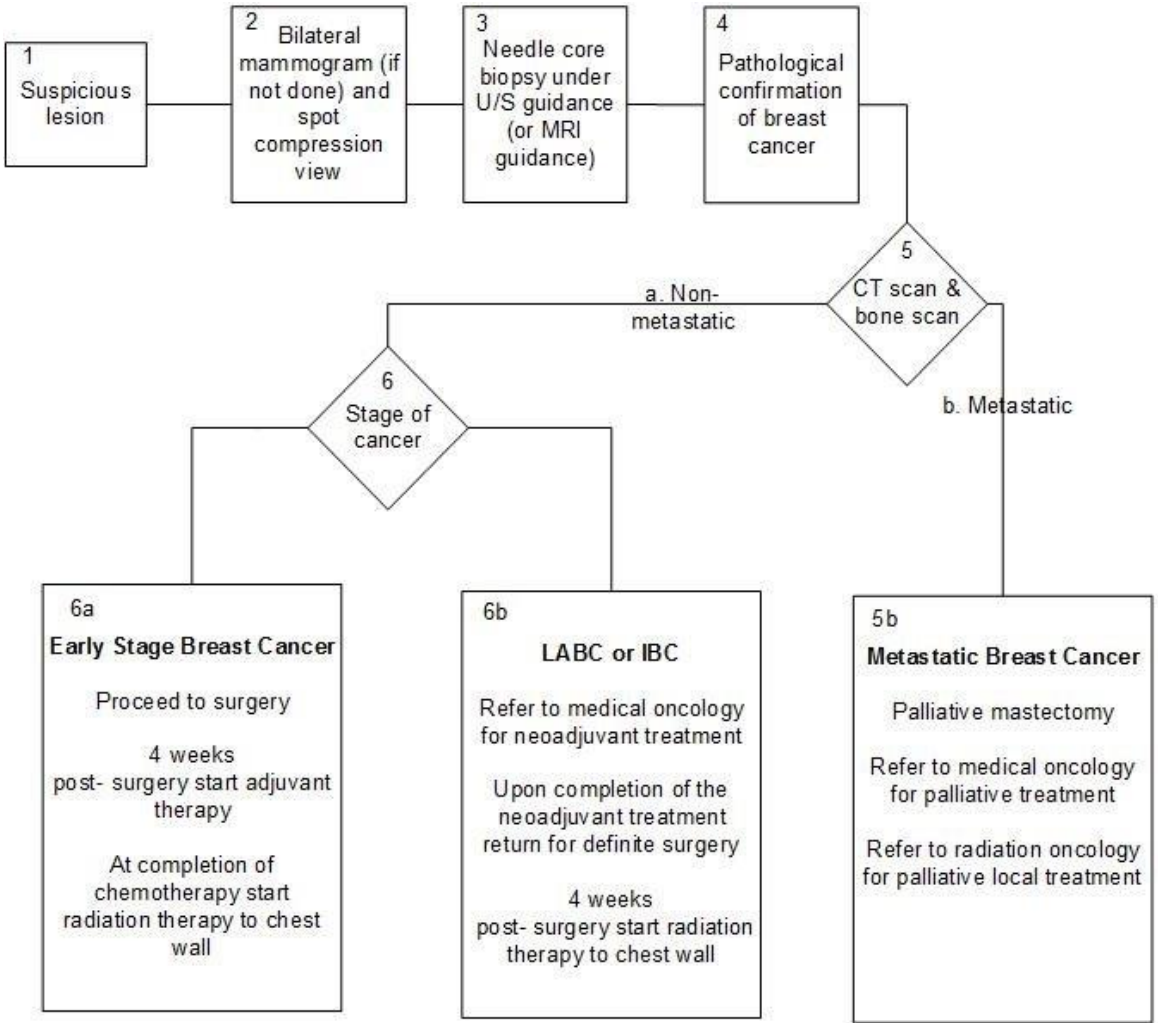
Appendix A: Diagnostic and Treatment Algorithm for Invasive Breast Cancer



Legend for the Diagnostic and Treatment Algorithm for Invasive Breast Cancer

1. *Suspicious lesion:* Patients usually enter the oncology system with a suspicious breast lesion either through a clinical presentation (found by self or family physician), through the breast screening program (finding on routine screening mammogram), or through an incidental finding (found on imaging while being investigated for a different health issue, such as CT or MRI of chest).
2. *Bilateral mammogram and spot compression views:* A bilateral mammogram (if not already completed) and a spot compression view will be performed to evaluate the suspicious lesion.
3. *Needle core biopsy under ultrasound (or MRI) guidance:* If the lesion is still considered to be suspicious at this stage, a needle core biopsy is performed under ultrasound-guidance (or MRI-guidance when difficulty visualizing the lesion) in an attempt to establish whether the lesion is malignant or benign.
4. *Pathological confirmation of breast cancer:* The family physician will often consult a surgeon while waiting for the results, or once a pathological diagnosis of breast cancer has been confirmed.
5. *CT scan and bone scan:* During the first visit, the surgeon will order a CT scan of the chest, abdomen and pelvis as well as, a nuclear medicine bone scan to be performed to complete the cancer staging. The results of these tests will determine whether the patient has:
6. *No evidence of metastatic disease:* See number 6.
7. *Evidence of metastatic disease:* If imaging provides evidence of distant metastatic spread from the breast cancer primary to the bones or other organs, the surgeon may

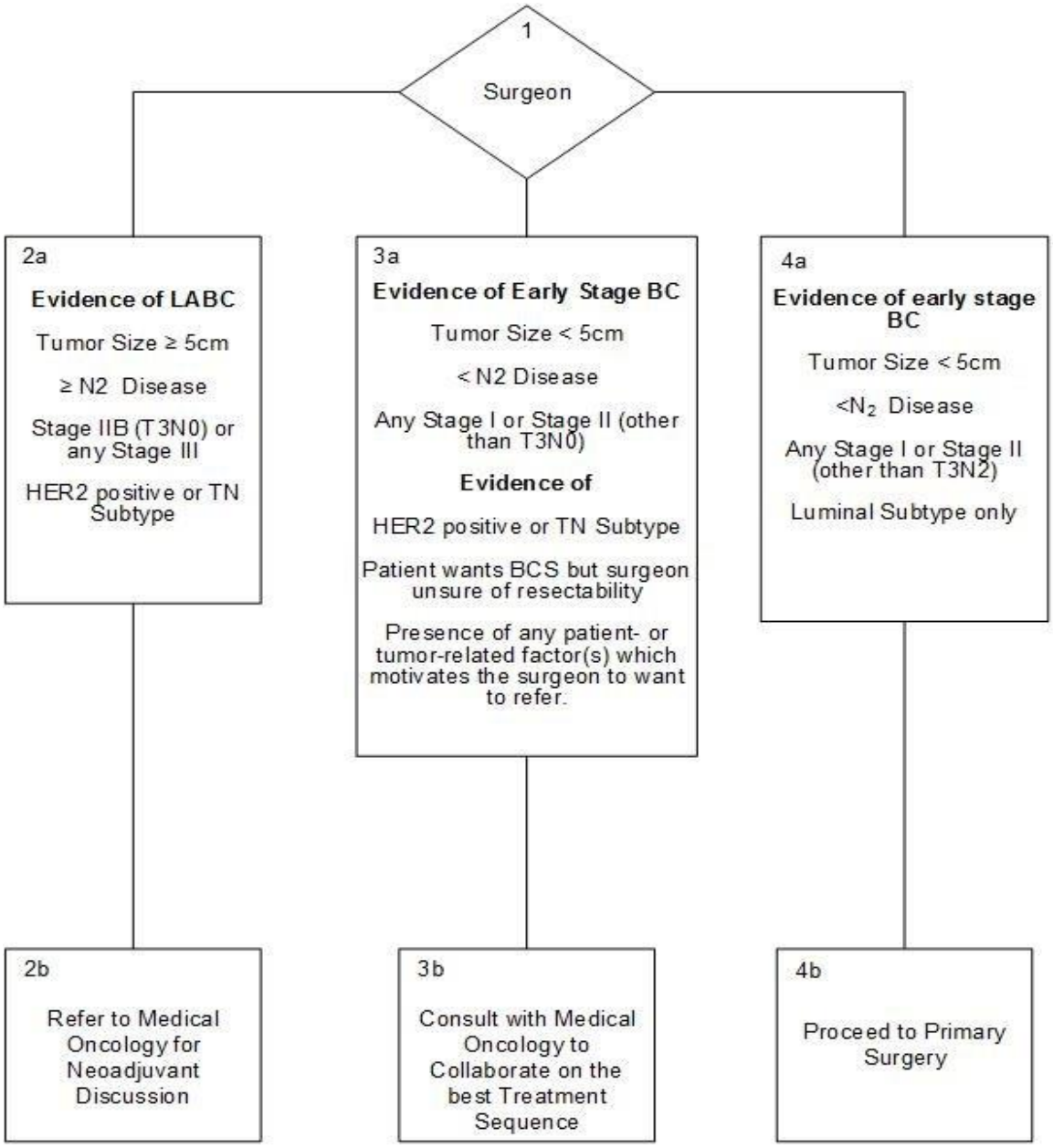
proceed with a palliative simple mastectomy and/or consult with both medical and radiation oncologists to determine the best treatment sequence with a palliative intent to alleviate symptoms and extend survival.

8. *No evidence of metastatic disease:* If imaging provides no definitive evidence of metastatic disease, the surgeon must determine to the best of her/his ability the AJCC clinical stage of the cancer. This will help determine whether the patient has in situ disease only, or if the patient has invasive disease which is either early stage or locally advanced/inflammatory breast cancer.

a. *Early stage breast cancer:* If the surgeon determines the patient has early-stage breast cancer, then the patient will proceed to undergo adjuvant therapy consisting of definitive surgery first, followed by chemotherapy and/or endocrine therapy (for 5-10 years) post-operatively, followed by chest wall radiation therapy if indicated.

b. *Locally advanced or inflammatory breast cancer:* If the surgeon determines the patient has locally advanced or inflammatory breast cancer, then the surgeon should refer the patient immediately to see a medical oncologist. If warranted, neoadjuvant chemotherapy or endocrine therapy will begin quickly, and the tumor will be assessed frequently for response. Sufficient tumor response after 4 to 6 cycles will be followed by definitive surgery, and then chest wall radiation therapy four week post-operatively. If there is little or no tumor response to the first treatment regimen after one or two cycles, the treatment can be altered or switched. Endocrine therapy will continue following the completion of radiation therapy for five to ten years, as directed.

Appendix B: Surgeon's Decision to Refer Algorithm



Legend for Surgeon's Decision to Refer for Non-Metastatic Invasive Breast Cancer

1. *Surgeon:* The surgeon must decide from the clinical, radiological and pathological evidence whether the patient has early stage breast cancer or has locally advanced/inflammatory breast cancer.

2a. *Locally advanced breast cancer or inflammatory breast cancer:* The surgeon would regard those patients with a clinical tumor size of ≥ 5 cm, and/or ≥ clinical N2 lymph node involvement, and/or a clinical AJCC stage IIB (T3N0) or any stage III breast cancer, with or without a HER2 positive or triple negative subtype on needle core biopsy to have locally advanced breast cancer. A patient with a clinical and pathological confirmation of inflammatory breast cancer will be regarded so by the surgeon.

2b. *Referral to Medical Oncology:* If the patient has been confirmed to have locally advanced breast cancer or inflammatory breast cancer as stipulated, the surgeon must refer the patient to the medical oncology discipline for a discussion about neoadjuvant therapy. The surgeon, using independent medical judgement, may decide to forego the neoadjuvant referral only in certain circumstances. One of these circumstances include when the patient's frailty or pre-existing co-morbidities impose an unacceptable mortality risk. Another would be when the patient refuses any treatment at all or will accept only surgical intervention. The surgeon must advise the patient of the risks of refusing some, or all, therapy and assure the patient that should change his/her mind the option of referral will still be open though the outcomes may not be assured.

3a. *Early stage breast cancer with extenuating circumstances:* The surgeon would regard patients to have early stage breast cancer if the patient had a clinical tumor size of <

5cm, and/or clinical N0 or N1 disease, and/or any clinical AJCC stage I or stage II (except T3 N0). However, patients with early breast cancer who have extenuating circumstances that may require neoadjuvant referral would include those with one or more of these clinical findings:

- a HER2 positive or triple negative subtype on needle core biopsy
- patient requests breast conserving surgery (BCS) but surgeon is unsure of resectability
- presence of any patient- or tumor-related factor(s) which may motivate the surgeon to refer (e.g., young age of patient, questionable clinical tumor size, grade 3 tumor, multifocal/multicentric disease).

3b. *Collaborate with a medical oncologist:* If the patient has any of the clinical findings listed in 3a, then the surgeon should contact a medical oncologist to present the case and come to some consensus of the best treatment sequence to initiate for the benefit of the patient.

4a. *Early stage breast cancer:* If the patient has a clinical tumor size of < 5cm, and/or clinical N0 or N1 disease, and/or any clinical AJCC stage I or stage II (except T3 N0) with or without a luminal subtype on needle core biopsy, then the surgeon must regard these cases as early stage breast cancer.

4b. *Proceed to primary surgery:* If the patient has no clinical indications which suggest the need for neoadjuvant referral than the surgeon must proceed to perform surgery has the primary treatment modality followed by a referral for adjuvant therapy approximately 4 weeks post-operatively